

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 May 2001 (03.05.2001)

PCT

(10) International Publication Number
WO 01/30778 A1

(51) International Patent Classification⁷: **C07D 417/04**,
471/04, A61K 31/437, 31/4436 // (C07D 471/04, 235:00,
221:00)

(74) Agent: **BECKER, Konrad**; Novartis AG, Corporate
Intellectual Property, Patent and Trademark Department,
CH-4002 Basel (CH).

(21) International Application Number: **PCT/EP00/10528**

(22) International Filing Date: 25 October 2000 (25.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9925441.9 27 October 1999 (27.10.1999) GB
9926173.7 4 November 1999 (04.11.1999) GB

(71) Applicant (for all designated States except AT, US): **NO-
VARTIS AG** [CH/CH]; Schwarzwaldallee 215, CH-4058
Basel (CH).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for AT only): **NOVARTIS-ERFINDUNGEN
VERWALTUNGSGESELLSCHAFT M.B.H.** [AT/AT];
Brunner Strasse 59, A-1230 Vienna (AT).

Published:

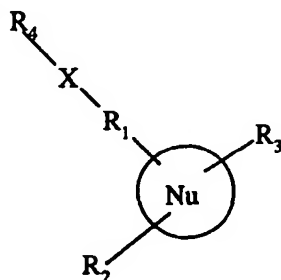
— With international search report.

(72) Inventor; and

(75) Inventor/Applicant (for US only): **RÉVÉSZ, László**
[CH/CH]; Ob dem Fichtenrain 7, CH-4106 Therwil (CH).

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: **THIAZOLE AND IMIDAZO [4,5-B] PYRIDINE COMPOUNDS AND THEIR PHARMACEUTICAL USE**



(I)

(57) Abstract: Compounds of formula (I) and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof, wherein the symbols are as defined are MAP kinase inhibitors, useful pharmaceutically for treating TNF α and IL-1 mediated diseases such as rheumatoid arthritis and diseases of bone metabolism, e.g. osteoporosis.

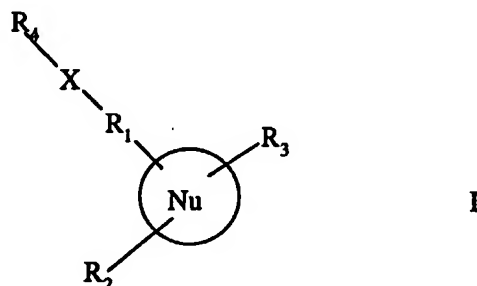
WO 01/30778 A1

- 1 -

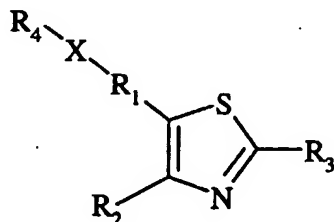
THIAZOLE AND IMIDAZO[4,5-B]PYRIDINE COMPOUNDS AND THEIR PHARMACEUTICAL USE

This invention relates to heterocyclic compounds, in particular to thiazoles and imidazopyridines and to their use for treating TNF α and IL-1 mediated diseases such as rheumatoid arthritis and diseases of bone metabolism, e.g. osteoporosis.

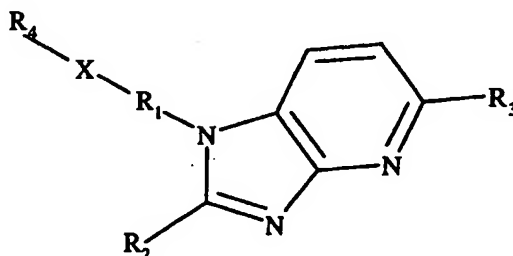
Accordingly the present invention provides a compound of formula I



wherein Nu is a heterocyclic nucleus selected from a thiazole in which the R₁, R₂ and R₃ substituents are disposed as indicated below



and an imidazo[4,5-b]pyridine in which the R₁, R₂ and R₃ substituents are disposed as indicated below



wherein

R₁ is pyrimidyl or pyridyl;

X is -NR₆-Y-, -O- or -S-,

where R₆ is H, C₁-C₄alkyl, C₃-C₈cycloalkyl, C₃-C₈cycloalkylC₁-C₃alkyl, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, C₇-C₁₉aralkyl or C₄-C₁₉heteroaralkyl, and -Y- is C₁-C₄alkylene or a direct bond;

R₂ is phenyl, optionally substituted by one or more substituents, each of which is independently selected from

halo,

CF₃,

cyano,

amido or thioamido which is optionally mono- or di-N-substituted by C₁-C₄alkyl or the N atom of which forms a 5-7 membered heterocyclic ring optionally containing an additional hetero atom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted,

carboxylate or thiocarboxylate optionally in the form of an optionally halo-substituted C₁-C₁₀alkoxy, C₂-C₁₀alkenoxy, C₂-C₁₀alkynoxy, C₃-C₇cyclalkoxy, C₅-C₇cycloalkenoxy, aryloxy, arylalkoxy, heteroaryloxy or heteroarylalkoxy ester, optionally mono- or di-C₁-C₄alkyl-substituted-C₀-C₁alkyl optionally C₁-C₄alkyl- or C₃-C₅ cycloalkyl-substituted-carbonyl or -thiocarbonyl,

optionally halo-substituted-C₁-C₄alkoxy, C₂-C₄alkenoxy, C₂-C₄alkynoxy, C₃-C₅cycloalkoxy or C₃-C₅cyclothioalkoxy,

optionally halo substituted C₁-C₄ alkyl,

oxycarbonyl or optionally N-C₁-C₄alkyl-substituted aminocarbonyl both of which are optionally C₁-C₄alkyl or C₃-C₅cycloalkyl substituted (including thiocarbonyl analogues thereof),

optionally mono- or di-C₁-C₄alkyl-substituted-C₀-C₁alkylamine which is optionally mono-or di-N-C₁-C₄ alkyl substituted,

optionally mono- or di-C₁-C₄alkyl-substituted-C₀-C₁alkyl optionally N-C₁-C₄alkyl-substituted amino-carbonyl or -thiocarbonyl,

optionally N-C₁-C₄alkyl-substituted amino-sulphinyl or -sulphonyl optionally substituted by

optionally mono- or di-N-C₁-C₄alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted, or

sulphinyl or sulphonyl optionally substituted by

optionally halo-substituted-C₁-C₄alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, optionally mono- or di-C₁-C₄alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted;

R₃ is H, amino, C₁-C₁₀alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₈heterocycloalkyl, C₆-C₁₈aryl, or C₃-C₁₈heteroaryl each of which is optionally substituted by up to 4 substituents separately selected from C₁-C₄alkyl, halogen, halo-substituted-C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, C₁-C₄alkylthio, C₆-C₁₈aryl, C₃-C₁₈ heteroaryl, C₆-C₁₈arylC₁-C₄alkyl, C₃-C₁₈ heteroarylC₁-C₄alkyl, C₃-C₁₈heterocycloalkyl or optionally mono- or di-C₁-C₄alkyl substituted amino or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally a further hetero atom selected from O, S or N, all of which are further optionally substituted halo, hydroxy, C₁-C₄alkyl, C₁-C₄alkoxy or C₁-C₄alkoxycarbonyl;

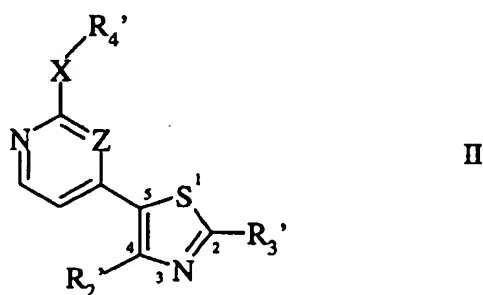
R₄ is C₁-C₁₀alkyl, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, or C₃-C₁₂cycloalkyl optionally substituted by up to 3 substituents separately selected from C₁-C₄alkyl, halogen, halo-substituted- C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, C₁-C₄alkylthio, optionally mono- or di-C₁-C₄alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof .

Above and elsewhere in the present description the terms halo or halogen denote I, Br, Cl or F.

Above and elsewhere in the present description the terms such as "C₃-C₁₈heteroaryl, C₄-C₁₉heteroaralkyl and C₃-C₁₈heterocycloalkyl" denote heteroaryl, heteroaralkyl or heterocycloalkyl substituents comprising at least 3 ring atoms, at least one of which is a hetero atom, e.g. N, O or S, and which in the case of C₄-C₁₉heteroaralkyl groups are attached via an alkylene moiety comprising at least 1 carbon atom.

In particular embodiments the invention provides a compound of formula II



wherein

Z is N or CH;

X is -NR₆-Y-, -O- or -S-,

where R₆ is H, C₁-C₄alkyl, C₃-C₈cycloalkyl, C₃-C₈cycloalkylC₁-C₃alkyl, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, C₇-C₁₉aralkyl or C₄-C₁₉heteroaralkyl, and -Y- is C₁-C₄alkylene or a direct bond ;

R₂' is phenyl, optionally substituted by one or more substituents, each of which is independently selected from halo, CF₃, cyano, amido or thioamido, carboxylate or thiocarboxylate, C₁-C₄alkoxy, C₁-C₄alkyl, or NH₂ which is optionally mono-or di-C₁-C₄alkyl substituted;

R₃' is H, C₁-C₁₀alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₈heterocycloalkyl, C₆-C₁₈aryl, or C₃-C₁₈heteroaryl each of which is optionally substituted by up to 4 substituents separately selected from C₁-C₄alkyl, halogen, halo-substituted-C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, C₁-C₄alkylthio, or optionally mono-or di-C₁-C₄alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N;

R_4' is C_6 - C_{18} aryl, C_3 - C_{18} heteroaryl, or C_3 - C_{12} cycloalkyl each of which is optionally substituted by up to 4 substituents separately selected from C_{1-4} alkyl, halogen, halo-substituted- C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, or optionally mono-or di- C_{1-4} alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

When R_3' is aryl, it is preferably heteroaryl, e.g. pyridyl (e.g. 4-pyridyl) or pyrazyl, each optionally substituted, e.g. by 2 substituents, separately selected from C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, or optionally mono-or di- C_{1-4} alkyl substituted amino.

When R_3' is cycloalkyl it is preferably C_3 - C_8 , especially C_5 - C_6 cycloalkyl (e.g. cyclohexyl), optionally substituted, e.g. by 1 or 2 substituents, separately selected from C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, or optionally mono-or di- C_{1-4} alkyl substituted amino.

When R_3' is heterocycloalkyl it is preferably N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom, e.g. N or O, and is optionally substituted, e.g. by 1 or 2 substituents, separately selected from C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, or optionally mono-or di- C_{1-4} alkyl substituted amino.

When R_4' is aryl it is preferably phenyl. When R_4' is cycloalkyl, it is preferably C_3 - C_7 cycloalkyl, e.g. cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl. R_4' may be unsubstituted or substituted, conveniently mono-substituted, e.g. phenyl conveniently meta or para substituted, by halogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy or optionally mono- or di- C_{1-4} alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N.

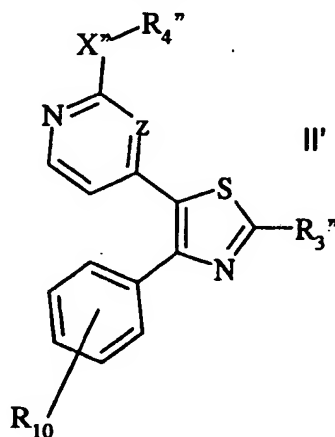
When Y is C_{1-4} alkylene, it is preferably C_{1-2} alkylene, and is optionally substituted, e.g. by C_{1-4} alkyl (e.g. methyl), halogen, hydroxy, C_{1-4} alkoxy, or amino.

More preferably R'_2 is phenyl substituted, preferably mono- or di-substituted, by halogen or a halogen-containing group, e.g. 4-fluorophen-1-yl, or 3- CF_3 , 3-Cl, or 3,4-difluoro substituted phenyl.

More preferably R'_3 is H, C_1 - C_6 alkyl, phenyl, pyridyl, morpholinyl, piperidyl, piperazyl, or optionally mono- or di- C_{1-4} alkyl substituted amino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from C_1 - C_4 alkyl, halogen, hydroxy, C_1 - C_4 alkoxy, or optionally mono- or di- C_1 - C_4 alkyl substituted amino.

Preferably X is -NH- Y' -, -O- or -S-, where Y' is - CH_2 -, - CH_2 - CH_2 -, -CH(CH_3)- or a direct bond

Thus in preferred embodiments the invention provides a compound of formula II'



wherein

R_4'' is phenyl or C_3 - C_7 cycloalkyl each of which is optionally mono-substituted by halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, hydroxy, trihalomethyl or optionally mono- or di- C_1 - C_4 alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N;

R_{10} is halogen, cyano, amido, thioamido, amino or C_1 - C_4 alkyl;

R_3'' is H, C_1 - C_4 alkyl, phenyl, pyridyl, morpholinyl, piperidyl, piperazyl, or optionally mono- or di- C_{1-4} alkyl substituted amino, each of which is optionally substituted, e.g. by up

to 2 substituents, separately selected from C₁-C₄alkyl, halogen, hydroxy, C₁-C₄alkoxy, or optionally mono-or di-C₁-C₄alkyl substituted amino;

Z is N or CH and

X'' is -NH-Y'-, -O- or -S-, where Y' is -CH₂-, -CH₂-CH₂-, -CH(CH₃)- or a direct bond, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

Preferably R₄'' is unsubstituted or monosubstituted by halogen, C₁-C₄alkyl (e.g. methyl), C₁-C₄alkoxy (e.g. methoxy), hydroxy or CF₃.

Preferably R₁₀ is halogen, e.g. F.

Preferably X'' is -NH-Y' where Y' is -CH(CH₃)-.

The Invention includes the following compounds:

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-methyl-piperidine-1-yl)thiazole;

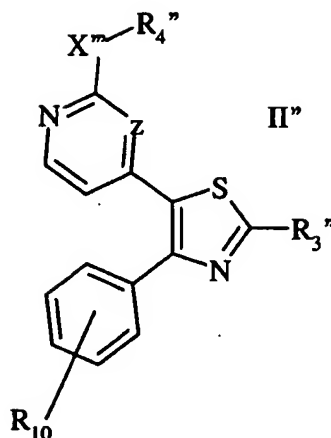
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-NH-piperidine-1-yl)thiazole;

4-(4-Fluorophenyl)-2-(4-methylpiperidine-1-yl)-5-(2-[cyclopropyl-methyl]amino-4-pyridinyl)thiazole and

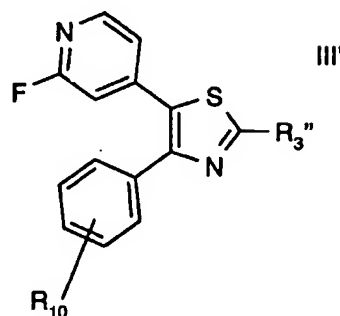
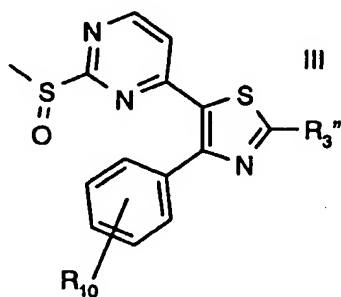
4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole;

The novel thiazoles of the invention, in particular the compounds of formulae II and II' and the specific compounds listed above are hereinafter referred to "Agents of the Invention".

Agents of the Invention of formula II''

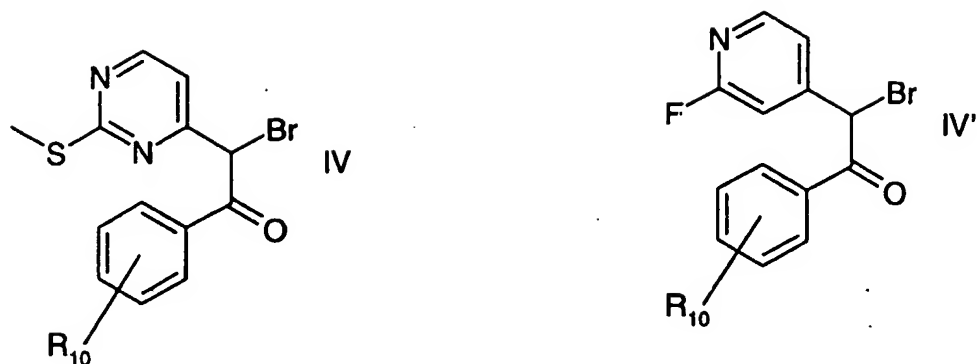


wherein R_3'' , R_5'' , R_{10} and Z are as previously defined and X''' is $-NH-$, may be prepared by reacting the corresponding precursor compound of formula III or III'



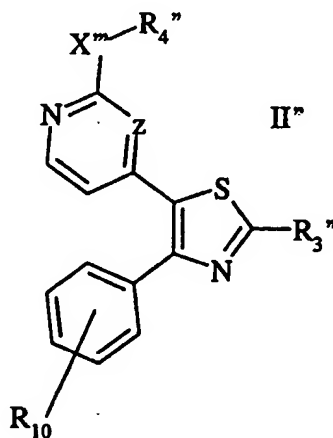
wherein R_3'' and R_{10} are as previously defined, with the corresponding $R_4''-NH_2$ derivative. For example, the reaction may be carried out by refluxing the reactants in an organic solvent, e.g. dichloroethane, e.g. in the presence of diethoxytrifluoroborane. Thereafter, if desired, the compound of Formula II' obtained may be converted into a further compound of Formula II' or otherwise treated as required.

The precursor compound of formula III may be prepared by controlled oxidation of the corresponding 5(2-methylthio-4-pyrimidinyl)-4-phenylthiazole, e.g. employing an oxidising agent such as mCPBA (meta chloroperbenzoic acid), conveniently in an organic solvent such as methylene chloride. The corresponding 5(4-pyrimidinyl/pyridinyl)-4-phenylthiazole compound may be prepared by contacting the corresponding acetophenone precursor compound of formula IV or IV'

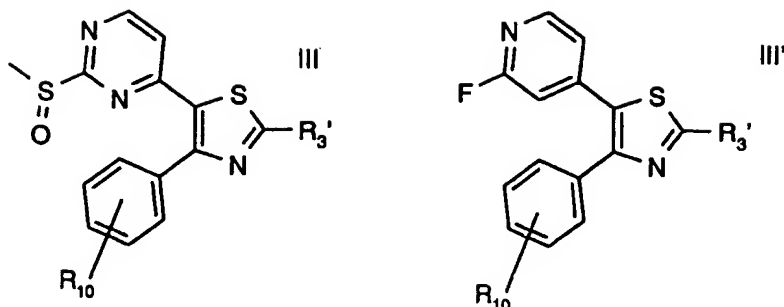


wherein R₁₀ is as defined above, with a corresponding thioamide of formula R₃'C(S)NH₂, typically at elevated temperature. The compounds of formula IV and IV' may be prepared by bromination of the corresponding acetophenone, e.g. 2-(2-methylthio-4-pyrimidinyl)acetophenone. The acetophenone precursor may be prepared by reacting the corresponding N-methoxy-N-methylbenzamide with the corresponding pyrimidine, e.g. 4-methyl-2-(methylthio) pyrimidine, for instance in a THF containing organic solvent with cooling.

Thus in a further aspect the invention includes a process for the preparation of a compound of formula II''

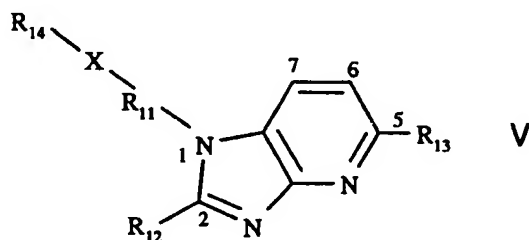


wherein R₃'', R₄'', R₁₀ and Z are as previously defined and X''' is -NH-, which comprises reacting the corresponding precursor compound of formula III or III'



wherein R₃' and R₁₀ are as previously defined, with the corresponding R₄'-NH₂ amine, and thereafter, if desired, converting the compound of formula II' obtained into a further compound of formula II'' or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof.

In further particular embodiments the invention provides a compound of formula V



wherein

R₁₁ is pyrimidyl;

X is -NR₆-Y-, -O- or -S-,

where R₆ is H, C₁-C₄alkyl, C₃-C₈cycloalkyl, C₃-C₈cycloalkylC₁-C₃alkyl, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, C₇-C₁₉aralkyl or C₄-C₁₉heteroaralkyl, and -Y- is C₁₋₄alkylene or a direct bond ;

R₁₂ is phenyl, optionally substituted by one or more substituents, each of which is independently selected from

halo,

CF₃,

cyano,

amido or thioamido which is optionally mono- or di-N-substituted by C₁-C₄alkyl or the N atom of which forms a 5-7 membered heterocyclic ring optionally containing

an additional hetero atom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted, carboxylate or thiocarboxylate optionally in the form of an optionally halo-substituted C₁-C₁₀alkoxy, C₂-C₁₀alkenoxy, C₂-C₁₀alkynoxy, C₃-C₇cyclalkoxy, C₅-C₇cycloalkenoxy, aryloxy, arylalkoxy, heteroaryloxy or heteroarylalkoxy ester, optionally mono- or di-C₁-C₄alkyl-substituted-C₀-C₁alkyl optionally C₁-C₄alkyl- or C₃-C₅ cycloalkyl-substituted-carbonyl or -thiocarbonyl, optionally halo-substituted-C₁-C₄alkoxy, C₂-C₄alkenoxy, C₂-C₄alkynoxy, C₃-C₅cycloalkoxy or C₃-C₅cyclothioalkoxy, optionally halo substituted C₁-C₄ alkyl, oxycarbonyl or optionally N-C₁-C₄alkyl-substituted aminocarbonyl both of which are optionally C₁-C₄alkyl or C₃-C₅cycloalkyl substituted (including thiocarbonyl analogues thereof), optionally mono- or di-C₁-C₄alkyl-substituted-C₀-C₁alkylamine which is optionally mono-or di-N-C₁-C₄ alkyl substituted, optionally mono- or di-C₁-C₄alkyl-substituted-C₀-C₁alkyl optionally N-C₁-C₄alkyl-substituted amino-carbonyl or -thiocarbonyl, optionally N-C₁-C₄alkyl-substituted amino-sulphinyl or -sulphonyl optionally substituted by

optionally mono- or di-N-C₁-C₄alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted, or

sulphinyl or sulphonyl optionally substituted by

optionally halo-substituted-C₁-C₄alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,

optionally mono- or di-N-C₁-C₄alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted;

R₁₃ is H, amino, C₁-C₁₀alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₈heterocycloalkyl, C₆-C₁₈aryl, or C₃-C₁₈heteroaryl all optionally substituted by up to 4 substituents separately selected from C₁-C₄alkyl, halogen, halo-substituted-C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, C₁-C₄alkylthio, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, C₆-C₁₈arylC₁-C₄alkyl, C₃-C₁₈heteroarylC₁-C₄alkyl, C₃-C₁₈heterocycloalkyl or optionally mono- or di-N-C₁-C₄alkyl substituted amino all of which are optionally substituted by halo, hydroxy, C₁-C₄alkyl, C₁-C₄alkoxy or C₁-C₄alkoxycarbonyl;

R₁₄ is C₁-C₁₀alkyl, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, or C₃-C₁₂cycloalkyl optionally substituted by up to 3 substituents separately selected from C₁-C₄alkyl, halogen, halo-substituted-C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, C₁-C₄alkylthio, optionally mono- or di-N-C₁-C₄alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof .

R₁₁ is preferably 4-pyrimidyl.

When R₁₃ is alkyl it is C₁-C₁₀alkyl, preferably C₁-C₆alkyl, optionally substituted, preferably with one or two substituents separately selected from hydroxy, C₁-C₄alkoxy, amino optionally mono-or disubstituted by C₁-C₄alkyl or N-heterocyclyl containing from 5 to 7 ring and optionally containing a further hetero atom (e.g. O, S or N).

When R₁₃ is aryl or heteroaryl either of which is optionally substituted by up to 4 substituents, R₁₃ may comprise one of the customary aryl or heteroaryl substituents in the art and may be substituted as is customary in the art; for instance as defined for the substituent R₃ of WO 93/03297. For instance, R₁₃ may comprise a phenyl, pyridyl or pyrimidyl, substituent optionally substituted by up to 5 substituents separately selected from C₁-C₄alkyl, halogen, halo-substituted C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, or optionally mono- or di-C₁-C₄alkyl substituted amino.

When R₁₃ is substituted amino it may be substituted by one or two substituents independently selected from C₁-C₄alkyl, C₆-C₁₈aryl, C₃-C₁₈ heteroaryl, C₆-C₁₈arylC₁-C₄alkyl, C₃-

C₁₈ heteroarylC₁-C₄alkyl, all of which are optionally substituted by halo, hydroxy, C₁-C₄alkyl, C₁-C₄alkoxy or C₁-C₄alkoxycarbonyl.

When R₁₃ is cycloalkyl it is preferably C₃-C₈, especially C₅-C₆cycloalkyl (e.g. cyclohexyl), optionally substituted, preferably with up to 2 substituents separately selected from C₁-C₄alkyl, halogen, hydroxy, C₁-C₄alkoxy, or optionally mono- or di-C₁-C₄alkyl substituted amino.

When R₁₃ is heterocycloalkyl it is preferably N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N, optionally substituted, e.g. by up to 2 substituents, selected from halogen, hydroxy, alkoxy, or optionally mono- or di-C₁-C₄alkyl substituted amino. For instance, R₁₃ may be an optionally substituted morpholino, piperazyl or piperidyl substituent.

When R₁₄ is aryl it is preferably phenyl. When R₁₄ is cycloalkyl, it is preferably C₃-C₇ cycloalkyl, e.g. cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl. R₁₄ may be unsubstituted or substituted, conveniently mono-substituted, e.g. phenyl conveniently meta or para substituted, by halogen, C₁-C₄alkyl, halo-substituted C₁-C₄alkyl, C₁-C₄alkoxy, hydroxy, optionally mono- or di-N-C₁-C₄alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N.

When -Y- is C₁-C₄ alkylene, it is preferably C₁-C₂ alkylene, and is optionally substituted, e.g. by C₁-C₄alkyl (e.g. methyl), halogen, hydroxy, C₁-C₄alkoxy, or amino.

Preferably R₁₂ is phenyl substituted with 1-3 substituents, preferably mono-substituted, selected from halogen, CN, halo-substituted alkyl, e.g. CF₃, C₁-C₄alkyl, or C₁-C₄alkoxy. Most preferably R₂ is phenyl mono-substituted by halogen, e.g. 4-fluorophenyl.

In particular embodiments R₁₃ is pyridyl, pyrimidyl, piperazyl, piperidyl, -NR₉R₁₀, -CH₂OH, -CH₂NR₁₅R₁₆, -CH₂CH₂R₁₅R₁₆, or Het-C₁₋₄alkyl-,

wherein

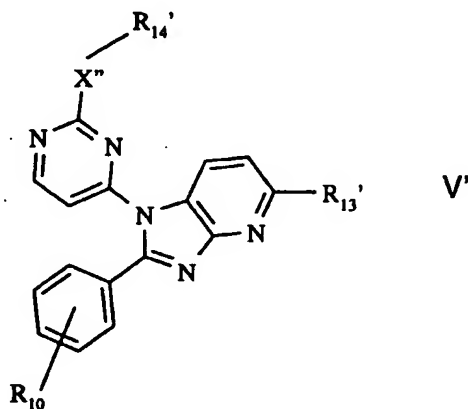
R_9 and R_{10} are separately selected from H, C_1 - C_4 alkyl, C_6 - C_{18} aryl, C_3 - C_{18} heteroaryl, C_6 - C_{18} aryl C_1 - C_4 alkyl, C_3 - C_{18} heteroaryl C_1 - C_4 alkyl all of which are optionally substituted by halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkoxycarbonyl,

R_{15} and R_{16} are separately selected from H or C_1 - C_4 alkyl, and

Het is N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom (e.g. O, S or N).

Preferably X is -NH-Y'-, -O- or -S-, where Y' is -CH₂-, -CH₂-CH₂-, -CH(CH₃)- or a direct bond. Most preferably X is NH-Y''-, where Y'' is -CH(CH₃)- or a direct bond.

Thus in preferred embodiments the invention provides a compound of formula V'



wherein

R_{14}' is phenyl or C_3 - C_7 cycloalkyl each of which is optionally mono-substituted by halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, hydroxy, trihalomethyl optionally mono- or di- N - C_1 - C_4 alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N;

R_{10} is halogen, CF_3 , C_1 - C_4 alkyl or C_1 - C_4 alkoxy;

R_{13}' is pyridyl, pyrimidyl, piperazinyl, piperidinyl, NR_9R_{10} , -CH₂OH, CH₂NR₁₅R₁₆, -CH₂CH₂R₁₅R₁₆, or Het- C_1 - C_4 alkyl-,

wherein

R_9 and R_{10} are separately selected from H, C_1 - C_4 alkyl, C_6 - C_{18} aryl, C_3 - C_{18} heteroaryl, C_6 - C_{18} aryl C_1 - C_4 alkyl, C_3 - C_{18} heteroaryl C_1 - C_4 alkyl all of which are optionally substituted by halo, hydroxy, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkoxycarbonyl,

R₁₁ and R₁₂ are separately selected from H or C₁-C₆alkyl, and

Het is N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom (e.g. O, S or N)

X'' is -NH-Y'-, -O- or -S-, where Y' is -CH₂-, -CH₂-CH₂-, -CH(CH₃)- or a direct bond, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

Preferably R₁₄' is phenyl or cyclopentyl, cyclobutyl or cyclopropyl.

Preferably R₁₀ is halogen.

Preferably X'' is -NH-Y'' where Y'' is -CH(CH₃)- or a direct bond.

The Invention includes the following compounds:

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(N,N-diethylamino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(morpholino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(isopropylamino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(pyrrolidino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(3-pyridyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-pyridyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-piperidinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-methyl-4-piperidinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-(2-hydroxy-2-methyl)propyl-4-piperidinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(benzylamino)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(morpholino)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(3-fluorophenyl amino)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(pyridyl-4-amino)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-ethoxycarbonyl piperidine-4-amino)imidazo[4,5-b]pyridine, and
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidine-4-amino)imidazo[4,5-b]pyridine.

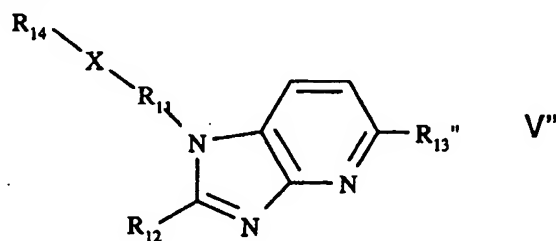
The novel imidazopyridines of the invention, in particular the compounds of formulae V and V' and the specific compounds listed above are hereinafter also referred to as "Agents of the Invention".

It will be appreciated that certain Agents of the Invention may contain at least 1 assymetric carbon atom; for instance when Y is substituted alkylene, e.g. when Y' is -CH(CH₃)- for the compounds of formula II' or V' above. The resulting diastereomers and enantiomers are encompassed by the instant invention. Preferably, however, e.g. for pharmaceutical use in accordance with the invention, the compounds of formula I, are provided in pure or substantially pure epimeric form, e.g. as compositions in which the compounds are present in a form comprising at least 90%, e.g. preferably at least 95% of a single epimer (i.e. comprising less than 10%, e.g. preferably less than 5% of other epimeric forms). Preferred epimeric compounds of formula I are described hereinafter in the Examples.

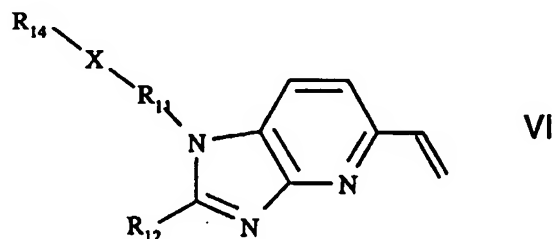
The Agents of the Invention which comprise free hydroxyl groups may also exist in the form of pharmaceutically acceptable, physiologically cleavable esters, and as such are included within the scope of the invention. Such pharmaceutically acceptable esters are preferably prodrug ester derivatives, such being convertible by solvolysis or cleavage under physiological conditions to the corresponding Agents of the Invention which comprise free hydroxyl groups. Suitable pharmaceutically acceptable prodrug esters are those derived from a carboxylic acid, a carbonic acid monoester or a carbamic acid, advantageously esters derived from an optionally substituted lower alkanolic acid or an arylcarboxylic acid.

Agents of the Invention may also exist in the form of pharmaceutically acceptable salts, and as such are included within the scope of the invention. Pharmaceutically acceptable salts include acid addition salts with conventional acids, for example, mineral acids, e.g., hydrochloric acid, sulfuric or phosphoric acid, or organic acids, for example, aliphatic or aromatic carboxylic or sulfonic acids, e.g., acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, hydroxymaleic, pyruvic, pantoic, methanesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; also amino acids, such as arginine and lysine. For compounds of the invention having acidic groups, for example, a free carboxy group, pharmaceutically acceptable salts also represent metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed with ammonia or suitable organic amines.

Agents of the Invention of Formula V''



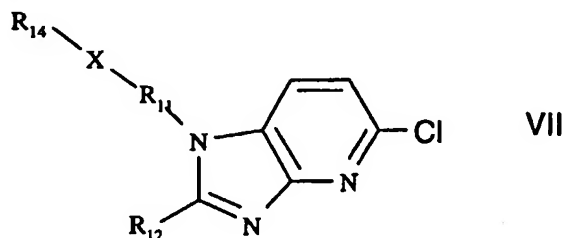
wherein R_{11} , R_{12} , R_{14} and X are as previously defined and R_{13}'' is $-\text{CH}_2-\text{CH}_2\text{NR}_{15}\text{R}_{16}$ or $-\text{CH}_2-\text{CH}_2\text{-Het}$ wherein R_{15} , R_{16} and Het are as defined above may be prepared by reacting a corresponding vinyl precursor compound of formula VI



wherein R_{11} , R_{12} , R_{14} and X are as previously defined, with the corresponding amine of formula $\text{HNR}_{15}\text{R}_{16}$ or N-heterocycloalkyl ring compound. For instance the reaction may be carried out by

refluxing the reactants, e.g. in acetic acid, followed by treatment with a mild base, e.g. Na_2CO_3 .

The precursor compound of formula VI may be prepared by reacting the corresponding 5-chloro-imidazopyridine of formula VII

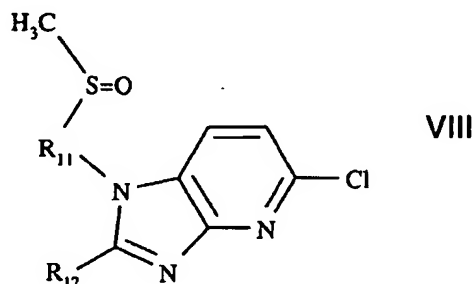


wherein R_{11} , R_{12} , R_{14} and X as are as previously defined, with a vinylating agent. For instance the chloro compound of formula VII is reacted with vinyltributylstannane in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ in xylene at elevated temperature, e.g. 160°C , under an inert atmosphere.

Agents of the Invention of formula V, wherein R_{13} is aryl or heteroaryl may be prepared from chloroprecursor compounds of formula VII, as defined above, by arylation or heteroarylation. For instance the compound of formula VII is heated with the corresponding trialkylstannyl-aryl or -heteroaryl, e.g. tributylstannylaryl- or trimethylstannyl-aryl or -heteroaryl, compound e.g. to about 150°C under an inert atmosphere.

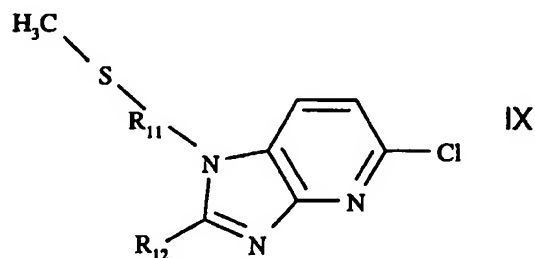
Agents of the Invention of formula V, wherein R_{13} is -N-heterocycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -NH-(C_1 - C_4 alkyl)-heterocycloalkyl, -NH-(C_1 - C_4 alkyl)-aryl, -NH-(C_1 - C_4 alkyl)-heteroaryl, or -NH-(C_1 - C_4 alkyl)-heterocycloalkyl may be prepared from chloroprecursor compounds of formula VII, as defined above, by coupling with the corresponding N-heterocycloalkyl compound or amine. The coupling reaction may be carried out using Buchwald chemistry. For instance, to a solution of the chloroprecursor compound of formula VII and a suitable ligand, e.g. BINAP, in an inert organic solvent such as xylene is added the N-heterocycloalkyl compound or amine together with an organic base, e.g. sodium tertiary butylate, and the reaction mixture heated, e.g. to 160°C for 10 minutes under argon; after which the product may be recovered by pouring the reaction mixture onto water and solvent extraction, e.g. with TBME.

The compounds of formula VII in which X is -NH- may be prepared by reacting the corresponding methylsulphiny compound of formula VIII



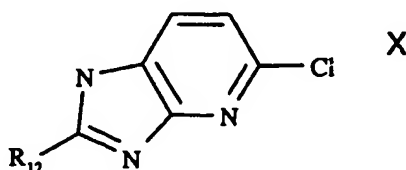
wherein R_{11} and R_{12} are as previously defined, with the corresponding amine of formula R_{14} - NH_2 . For instance, the reactants are mixed and heated, e.g. to $80^\circ C$ for 1h.

The methylsulphiny compound of formula VIII prepared by oxidation of the corresponding methylthio compound of formula IX.



wherein R_{11} and R_{12} are as previously defined; for instance, by treating the compound of formula IX in solution, e.g. $CH_2Cl_2/HOAc$ solution, with mCPBA, e.g. at $0^\circ C$ for 30 min., followed by treatment with mild base, e.g. Na_2CO_3 .

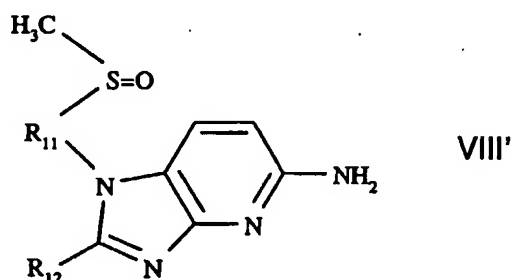
The methylthio compound of formula IX may be prepared by coupling the corresponding 1-H-imidazopyridine compound of formula X



wherein R_{12} is as defined above, with 2-methylthio-4-iodopyrimidine. For instance, $\text{KN}(\text{TMS})_2$ solution, e.g. in toluene, is added at 0°C to a solution of X, e.g. in DMF with mixing, and 2-methyl-4-iodopyrimidine solution e.g. in toluene, is added and the reaction mixture heated e.g. at 120°C for 20h.

The compound of formula X may be prepared by coupling 2,3-diamino-6-chloropyridine with the corresponding acid of formula $R_{12}\text{COOH}$; for instance, by treating a mixture of the reactants with polyphosphonic acid e.g. at 150°C for 6h, followed by neutralisation e.g. with cold concentrated aqueous NH_3 .

Compounds of formula V in which R_{13} is NH_2 may be prepared by reacting the corresponding methyl sulphonyl compound of formula VIII'



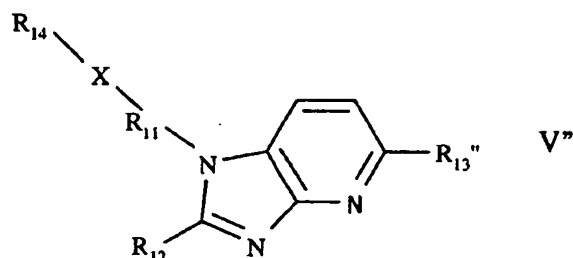
wherein R_{11} and R_{12} are as previously defined, with the corresponding amine of formula $R_{14}\text{-NH}_2$, for instance, as described above for the compound of formula VI. The compound of formula VIII' and precursors therefor may be prepared by analogy with the compound of formula VIII and the precursors thereof; for instance, as described above.

Agents of the Invention which are 5-(4-NH-1-piperazyl)imidazopyridines of formula V in which R_{13} is piperazyl and precursors therefor may be prepared by analogy to the preparation of the compound of formula VIII' and the precursors thereof. Conveniently the free nitrogen atom of the piperazine ring is protected e.g. with a tert. butoxycarbonyl residue, during precursor preparation as appropriate. 5-(4-NH-1-piperazyl)imidazopyridines of formula I may be converted

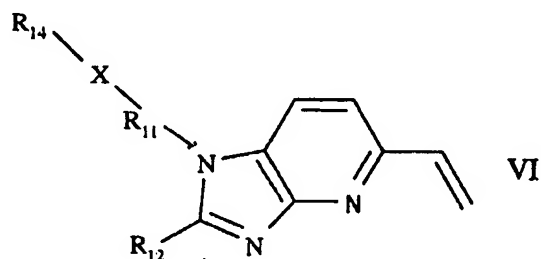
to 5-(4-substituted piperazyl)imidazopyridine Agents of the Invention as desired; for instance, as hereinafter described in the Examples.

Accordingly in a further aspect the invention provides a process for the production of

- (i) an Agent of the Invention of formula V''

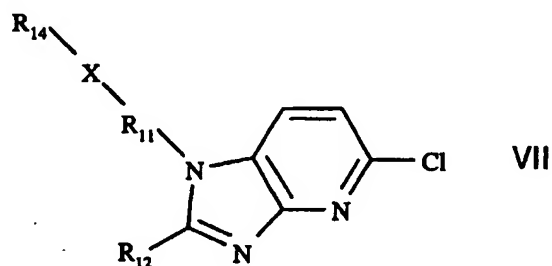


wherein R_{11} , R_{12} , R_{14} and X are as previously defined and R_{13}'' is $-\text{CH}_2-\text{CH}_2\text{NR}_{15}\text{R}_{16}$ or $-\text{CH}_2-\text{CH}_2\text{-Het}$ wherein R_{15} , R_{16} and Het are as previously defined comprising reacting a corresponding vinyl precursor of formula VI



wherein R_{11} , R_{12} , R_{14} and X are as previously defined with the corresponding amine of formula $\text{HNR}_{15}\text{R}_{16}$ or N-heterocycloalkyl ring compound;

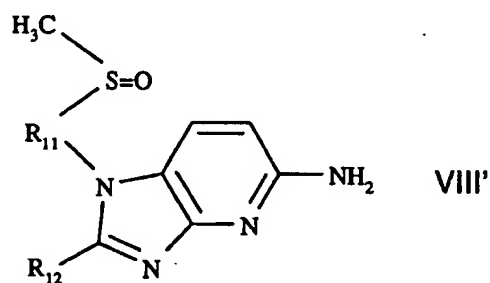
- (ii) an Agent of the Invention of formula V wherein R_{13} is aryl or heteroaryl comprising arylation or heteroarylation of a compound of formula VII



wherein R_{11} , R_{12} , R_{14} and X are as previously defined;

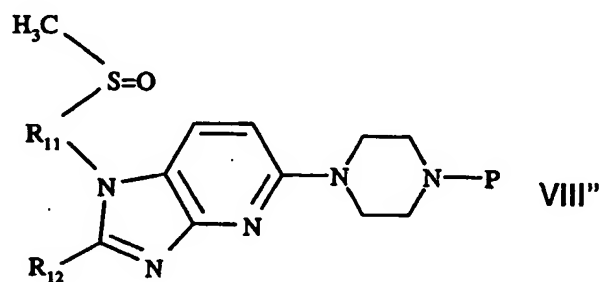
(iii) an Agent of the Invention of formula V wherein R_{13} is -N-heterocycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -NH-(C_1 - C_4 alkyl)-heterocycloalkyl, -NH-(C_1 - C_4 alkyl)-aryl, -NH-(C_1 - C_4 alkyl)-heteroaryl, or -NH-(C_1 - C_4 alkyl)-heterocycloalkyl comprising coupling a corresponding chloroprecursor compound of formula VII, as defined above, with the corresponding N-heterocycloalkyl compound or amine;

(iv) an Agent of the Invention of formula V in which R_{13} is $-NH_2$, comprising reacting the corresponding methyl sulphinyl compound of formula VIII'



wherein R_{11} , and R_{12} are as previously defined, with the corresponding amine of formula $R_{14}-NH_2$, and

(v) an Agent of the Invention of formula V in which R_{13} is piperazinyl, comprising reacting a corresponding methylsulphinyl compound of formula VIII''



wherein R_{11} and R_{12} are as previously defined and P is an N protecting group, with the corresponding amine of formula $R_{14}-NH_2$.

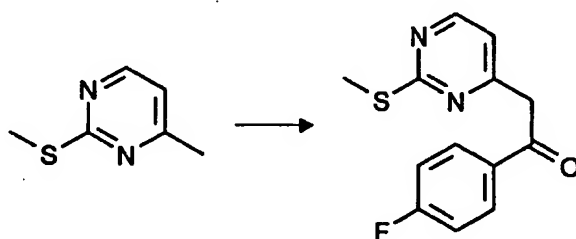
The synthesis of Agents of the Invention is further described in the following Examples.

EXAMPLES**Example 1 4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)thiazole****a) N-Ethoxycarbonylpiperidine-4-thiocarboxamide**

N-Ethoxycarbonylpiperidine-4-carboxamide (6g 30mmol) in toluene (300ml) is treated with Lawesson's reagent (6.1g 15mmol) at room temperature for 18h. The reaction mixture is evaporated and purified by SiO_2 chromatography (acetone/cyclohexane 20/80) to yield the title compound, which is recrystallised from hexanes (3.6g 52.5%)

$^1\text{H-NMR}$ (400MHz; CDCl_3): 1.28 (t, 3H); 1.72-1.83 (dq, 2H); 1.95 (d, 2H); 2.68-2.88 (m, 3H); 4.18 (q, 2H); 4.30 (bs, 2H); 6.92 (bs, 1H, NH); 7.51 (bs, 1H, NH)

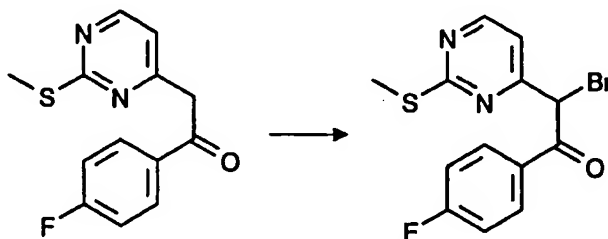
MS (m/z) CI: 217 (MH^+ , 50); 171 (100).

b) 4-Fluoro-2-(2-methylthio-4-pyrimidinyl)acetophenone

n-BuLi (10 ml of a 1.6 M solution in hexane; 12 mmol) is added at -78°C to a solution of diisopropylamine (2.48 ml; 17 mmol) in THF (15 ml) and stirred for 5 min. 4-Methyl-2-(methylthio)pyrimidine (2g; 14.5 mmol) dissolved in THF (2 ml) is added dropwise and stirred for 30 min at -78°C . 4-Fluoro-N-methoxy-N-methylbenzamide (2.66 g; 14.5 mmol) is dissolved in THF (3 ml) and added slowly to the reaction mixture. The mixture is warmed to r.t. within 45 min. and poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness to yield 2.5 g (65%) of yellow crystals after recrystallisation from tert.butyl methyl ether/hexane.

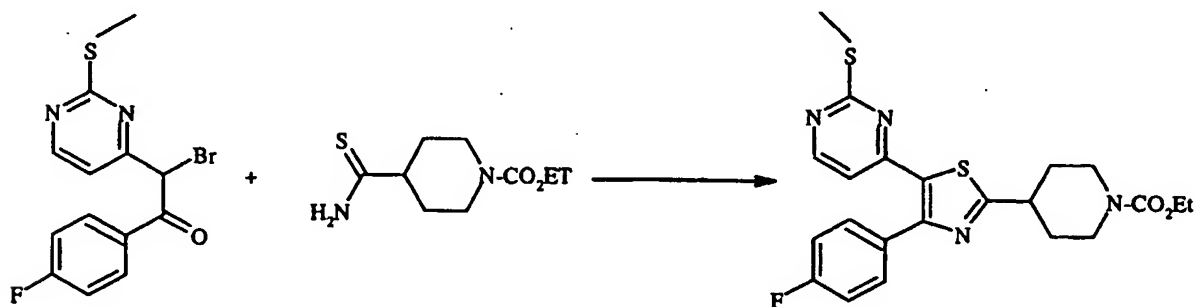
¹H-NMR (200 MHz CDCl₃): 3.00 (s, 3H); 6.30 (s, 1H; vinyl-H of enol); 7.00 (d, 1H); 7.50 (dd, 2H); 8.20 (dd, 2H); 8.7 (d, 2H). Due to pH-dependent keto-enol tautomerism, signals may be duplicated.

c) 4-Fluoro-2-bromo-2-(2-methylthio-4-pyrimidinyl)acetophenone



Bromine (1.22g; 7.6 mmol) in acetic acid (5.6 ml) is added to a solution of 4-Fluoro-2-(2-methylthio-4-pyrimidinyl)acetophenone (2g; 7.6 mmol) in acetic acid (40 ml). The initially thick precipitate is almost dissolved after 20 min., filtered and the filtrate evaporated to dryness. The residue is taken up in a saturated solution of NaHCO₃ and extracted three times with tert.butyl methyl ether. The combined organic phases are dried over Na₂SO₄ and evaporated to dryness to yield 2.6 g (100%) of a brown oil, which is used in the next step without purification.

d) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylthio-4-pyrimidinyl)thiazole



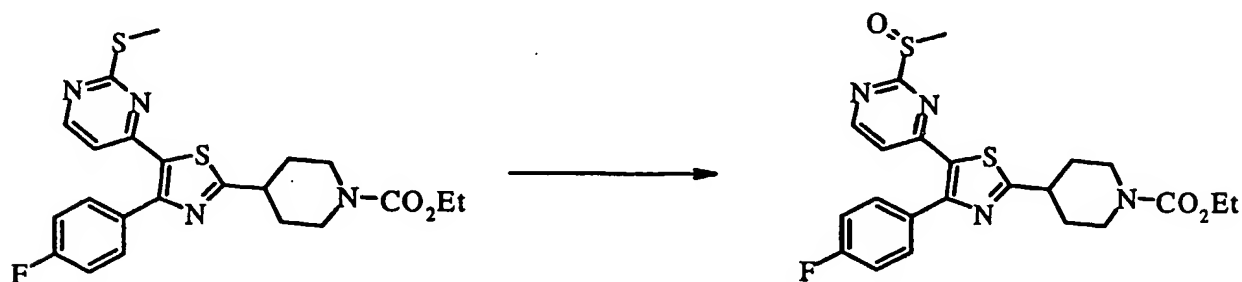
Na₂SO₄ (6.9g 40mmol) in DMF (100ml) is heated at 120°C for 10min. N-Ethoxycarbonyl-piperidine-4-thiocarboxamide (8.6g 40mmol) is added as a solid and heating continued for 5min.

2-Bromo-2-(2-methylthio-4-pyrimidinyl)-1-(4-fluorophenyl)ethanone (6.8g 20mmol) in DMF (20ml) is rapidly added within 3 seconds and stirring continued at 120°C for 10min. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na₂SO₄, filtered, evaporated to dryness and purified by SiO₂ chromatography (ethyl acetate/hexanes 5/95 to 10/90) to yield the title compound as yellow crystals (2.2g 24%)

¹H-NMR (400MHz; CDCl₃): 1.31 (t, 3H); 1.78-1.92 (dq, 2H); 2.21 (bd, 2H); 2.58 (s, 3H); 2.91-3.03 (bt, 2H); 3.18-3.28 (m, 1H); 4.20 (q, 2H); 4.25-4.40 (bs, 2H); 6.75 (d, 1H); 7.15 (t, 2H); 7.57 (dd, 2H); 8.31 (d, 1H).

MS (m/z) ESI: 459 (MH⁺, 100).

e) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylsulfinyl-4-pyrimidinyl)thiazole

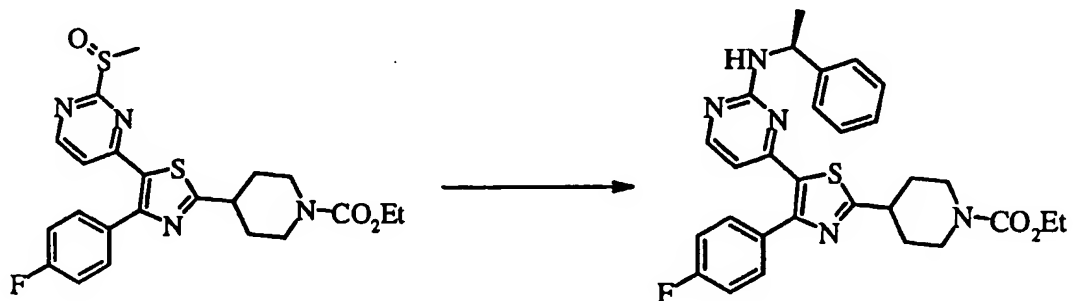


4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylthio-4-pyrimidinyl)thiazole (4.0g 8.7mmol) in CH₂Cl₂ (80ml) is treated with mCPBA (70% 2.1g 8.7mmol) at 0°C for 15min. The reaction mixture is poured on 2N Na₂CO₃ and extracted with CH₂Cl₂ three times. The combined organic phases were dried over Na₂SO₄, filtered, evaporated to dryness and purified by SiO₂ chromatography (acetone/hexanes 20/80 to 50/80) to yield the title compound (2.2g 53%) as a white foam.

¹H-NMR (400MHz; CDCl₃): 1.31 (t, 3H); 1.78-1.92 (dq, 2H); 2.21 (bd, 2H); 3.00 (s, 3H); 2.90-3.02 (m, 2H); 3.20-3.30 (bt, 1H); 4.18 (q, 2H); 4.25-4.40 (bs, 2H); 7.15 (d, 1H); 7.20 (t, 2H); 7.56 (dd, 2H); 8.63 (d, 1H).

MS (m/z) ESI: 475 (MH⁺).

f) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)thiazole

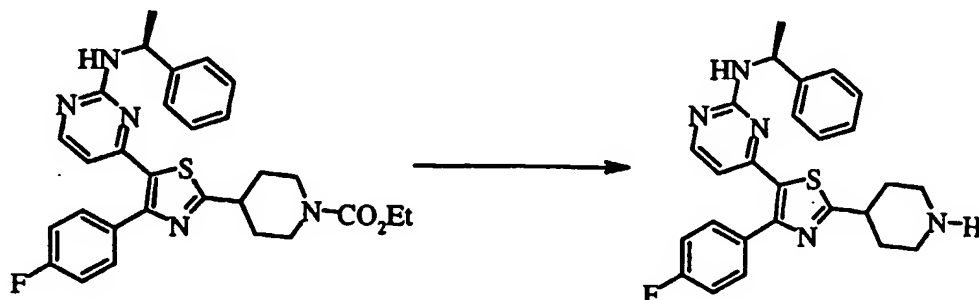


4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylsulfinyl)-4-pyrimidinyl)thiazole (2.2g 4.6mmol) and 1-(S)-phenylethylamine (2.2ml) are heated at 100°C for 1h. Purification over SiO₂ (acetone/cyclohexane 10/90 to 20/80) yielded the title compound as a pale yellow foam (2.4g 95%).

¹H-NMR (400MHz; CDCl₃): 1.31 (t, 3H); 1.51 (d, 3H); 1.75-1.88 (bq, 2H); 2.18 (bd (2H); 2.97 (bt, 2H); 3.20 (tt, 1H); 4.20 (q, 2H); 4.30 (bs, 2H); 5.17 (m, 1H); 5.46 (d, 1H, NH); 6.35 (d, 1H); 7.12 (t, 2H); 7.30-7.45 (m, 5H); 7.55 (dd, 2H); 8.08 (d, 1H).

MS (m/z) ESI: 523 (MH⁺, 100).

g) 4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)thiazole

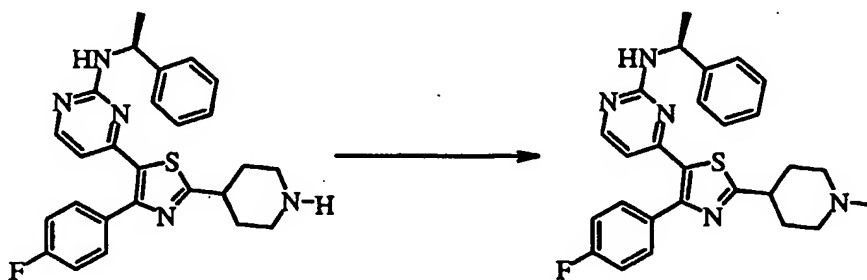


4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)thiazole (2.4g 4.5mmol) was dissolved in CHCl_3 (45ml) and treated with Me_3SiI (1.8ml 13.5mmol) at 60°C for 6h. The reaction mixture was combined with 6M HCl in propanol (18.5ml), homogenized by vigorous stirring, poured on 2N NaOH and extracted twice with CH_2Cl_2 . The combined organic phases were dried over Na_2SO_4 , filtered, evaporated to dryness and purified by SiO_2 chromatography (tert.butyl methyl ether /MeOH/ NH_3 conc. 95/4.5/0.5 to 80/18/2) to yield the title compound (1.8g 87%) as a white foam.

$^1\text{H-NMR}$ (400MHz; CDCl_3): 1.51 (d, 3H); 1.75-1.88 (bq, 2H); 2.18 (bd (2H); 2.82 (dt, 2H); 3.18 (tt, 1H); 3.25 (d, 2H); 5.17 (m, 1H); 5.45 (d, 1H, NH); 6.32 (d, 1H); 7.12 (t, 2H); 7.30-7.47 (m, 5H); 7.56 (dd, 2H); 8.07 (d, 1H).

MS (m/z) ESI: 460 (MH^+ , 100).

Example 2; 4-(4-Fluorophenyl)-2-(1-methylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl) thiazole

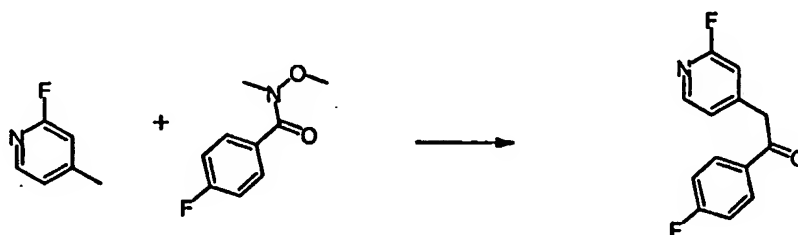


4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl) thiazole (575mg 1.25mmol) is dissolved in MeOH (12ml) and treated with an aqueous 36%-solution of formaldehyde (0.2ml 2.5mmol) and NaBH_4 (95mg 2.5mmol), which is added as a solid in 3 portions. After 30min at room temperature the reaction mixture is poured on water and extracted three times with ethyl acetate. The combined organic phases are dried over Na_2SO_4 , filtered, evaporated to dryness and purified by SiO_2 chromatography (tert.butyl methyl ether /MeOH / NH_3 conc. 95/4.5/0.5 to 90/9/1) to yield the title compound (600mg 85%) as pale yellow foam.

¹H-NMR (400MHz; CDCl₃): 1.51 (d, 3H); 1.88-2.01 (m, 2H); 2.08-2.25 (m, 4H); 2.48 (s, 3H); 2.97-3.08 (m, 3H); 5.18 (m, 1H); 5.48 (d, 1H, NH); 6.33 (d, 1H); 7.12 (t, 2H); 7.30-7.47 (m, 5H); 7.56 (dd, 2H); 8.05 (d, 1H).
MS (m/z) ESI: 474 (MH⁺, 100).

Example 3 4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole

a) 4-Fluoro-2-(2-fluoropyridin-4-yl)acetophenone

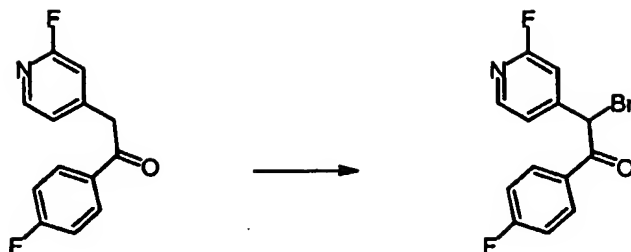


Diisopropylamine (0.93 ml; 6.55 mmol) in THF (6 ml) is cooled to -78 C and treated with nBuLi (3.8 ml; 6.08 mmol of a 1.6 M solution in hexane). 2-Fluoro-4-methylpyridine (620 mg; 5.4 mmol) is added dropwise and stirred under argon for 30 min. 4-Fluoro-N-methoxy-N-methylbenzamide (1 g; 5.46 mmol) is added dropwise in THF (0.5 ml) and the reaction mixture allowed to warm up to room temperature within 10 min. then poured on a saturated solution of NaCl and extracted with TBME three times. The combined organic phases are washed with water, dried over Na₂SO₄, filtered and evaporated to dryness to yield the title compound as pale yellow crystals. Purification by recrystallisation from hot TBME rendered the desired compound as white solid (630 mg; 50 %).

¹H-NMR (200 MHz; CDCl₃): 4.35 (s, 2H); 6.88 (s, 1H); 7.08-7.30 (m, 3H); 7.99-8.15 (dd, 2H); 8.20 (d, 1H).

MS (e/z) ESI: 233 (M⁺, 5); 123 (100).

b) 4-Fluoro-2-bromo-(2-fluoropyridin-4-yl)acetophenone

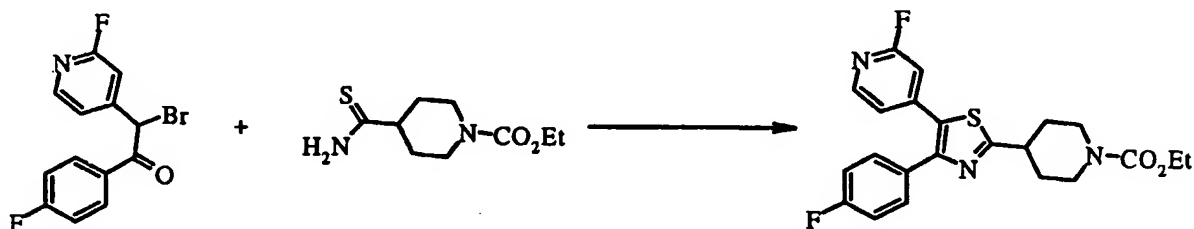


4-Fluoro-2-(2-fluoropyridin-4-yl)acetophenone (0.5 g; 2.1 mmol) dissolved in acetic acid (4 ml) is treated with bromine (0.34 g; 2.1 mmol) in acetic acid (1 ml) at room temperature for 2.5 h under stirring. The light brown solution is evaporated to dryness, dissolved in ether and extracted three times with diethyl ether. The combined organic phases are washed with a saturated solution of NaHCO₃, dried over Na₂SO₄, filtered and evaporated to dryness to yield the title compound as pale yellow oil (0.67 g; 100%).

¹H-NMR (200 MHz; CDCl₃): 6.15 (s, 1H); 7.10-7.38 (m, 4H); 8.08 (dd, 2H); 8.23 (d, 1H).

MS (e/z) ESI: 232 (M-Br); 204 (10); 203 (12); 123 (100).

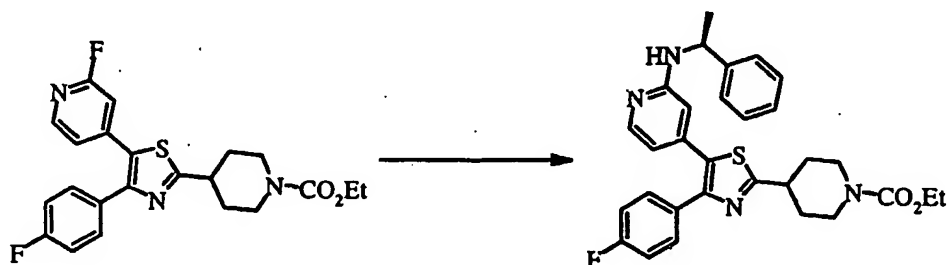
c) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-fluoro-4-pyridinyl)thiazole



2-Bromo-2-(2-fluoro-4-pyridyl)-1-(4-fluorophenyl)ethanone (2.5g 8.0mmol) and N-ethoxycarbonyl-piperidine-4-thiocarboxamide (2.1g 9.6mmol) are heated at 60°C in DMF (4ml) for 30min. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na₂SO₄, filtered, evaporated to dryness and purified by SiO₂ chromatography (ethyl acetate/cyclohexane 20/80 to 100/0) to yield the title compound as an oil (2.5g 70%)

MS (m/z) ESI: 430 (MH⁺)

d) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole

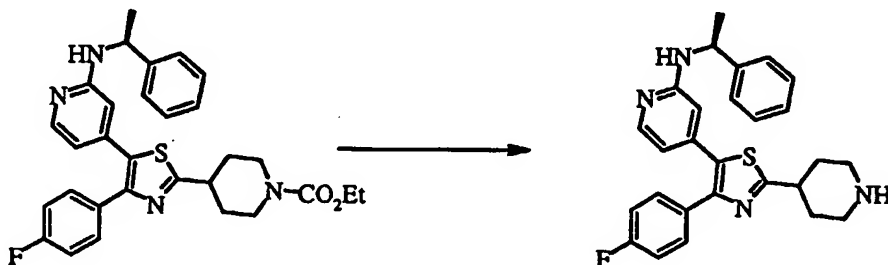


4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-fluoro-4-pyridinyl)thiazole (2.4g 5.5mmol) and 1-(S)-phenylethylamine (5.5ml) are heated to 195°C for 5h. The reaction mixture is evaporated and purified by SiO₂ chromatography (ethyl acetate/cyclohexane 20/80 to 30/70) to yield the title compound as a white foam (2.0g 67.3%)

¹H-NMR (400MHz; CDCl₃): 1.31 (t, 3H); 1.55 (d, 3H); 1.72-1.87 (m, 2H); 2.17 (d, 2H); 2.98 (bt, 2H); 3.15-3.23 (m, 1H); 4.18 (q, 2H); 4.30 (bs, 2H); 4.56 (m, 1H); 5.01 (d, 1H, NH); 6.15 (s, 1H); 6.50 (d, 1H); 6.95 (dd, 2H); 7.22-7.46 (m, 5H); 7.45 (dd, 2H); 8.03 (d, 1H).

MS (m/z) CI: 531 (MH⁺, 100).

e) 4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole



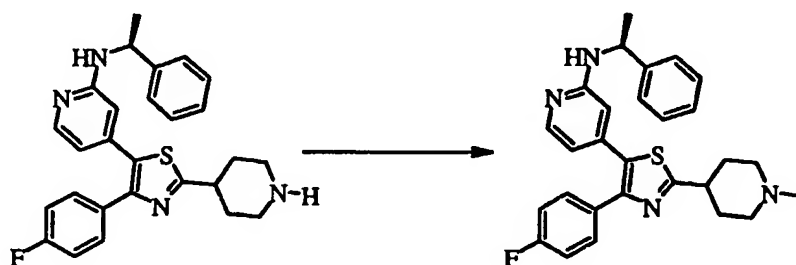
4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole (2g 3.7mmol) is dissolved in CHCl₃ (37ml) and treated with Me₃SiI (1.5ml 11.1mmol) at 60°C for 5h. A second portion of Me₃SiI (0.75ml 5.55mmol) was added and stirring continued for another 3h at 60°C. The reaction mixture was combined with 6M HCl in propanol (15ml), homogenized by vigorous stirring, poured on 2N NaOH and extracted twice

with CH_2Cl_2 . The combined organic phases were dried over Na_2SO_4 , filtered, evaporated to dryness and purified by SiO_2 chromatography (tert.butyl methyl ether / MeOH / NH_3 conc. 80/18/2) to yield the title compound (1.2g 71%) as a white foam.

$^1\text{H-NMR}$ (400MHz; CDCl_3): 1.53 (d, 3H); 1.77 (bs, 3H); 2.17 (bd, 2H); 2.78 (bt, 2H); 3.15 (bt, 1H); 3.35 (bd, 2H); 4.55 (m, 1H); 5.00 (d, 1H, NH); 6.17 (s, 1H); 6.50 (d, 1H); 6.97 (bt, 2H); 7.20-7.37 (m, 5H); 7.45 (bt, 2H); 8.02 (d, 1H).

MS (m/z) CI: 459 (MH⁺)

Example 4: 4-(4-Fluorophenyl)-2-(1-methylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole



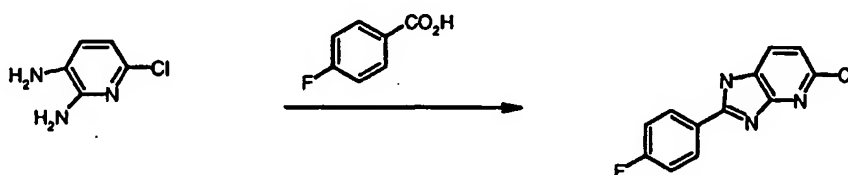
4-(4-Fluorophenyl)-2-(4-piperidinyl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole (500mg 1.09mmol) is dissolved in MeOH (11ml) and treated with an aqueous 36%-solution of formaldehyde (0.17ml 2.18mmol) and NaBH_4 (83mg 2.18mmol), which is added as a solid in 3 portions. After 30min at room temperature the reaction mixture is poured on water and extracted three times with ethyl acetate. The combined organic phases are dried over Na_2SO_4 , filtered, evaporated to dryness and purified by SiO_2 chromatography (tert.butyl methyl ether / MeOH / NH_3 conc. 95/4.5/0.5) to yield the title compound (550mg 86%) as pale yellow foam.

$^1\text{H-NMR}$ (400MHz; CDCl_3): 1.53 (d, 3H); 1.83-1.98 (m, 2H); 2.07-2.20 (m, 4H); 2.35 (s, 3H); 2.98 (bd, 3H); 4.55 (m, 1H); 4.98 (d, 1H, NH); 6.15 (s, 1H); 6.50 (d, 1H); 6.98 (t, 2H); 7.22-7.35 (m, 5H); 7.45 (dd, 2H); 8.02 (d, 1H).

MS (m/z) ESI: 473 (MH⁺)

Example 5: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidino-N-2-ethyl)imidazo-[4,5-b]pyridine

a) 5-Chloro-2-(4-fluorophenyl)imidazo[4,5-b]pyridine

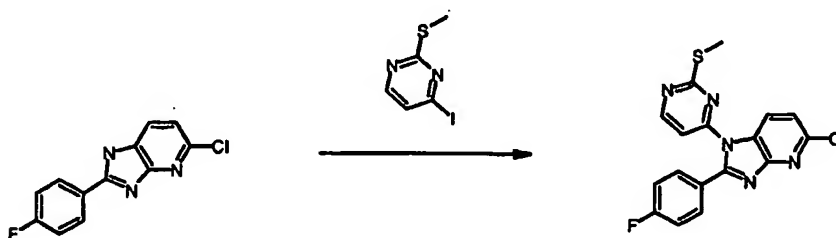


2,3-Diamino-6-chloropyridine (Davos-Bulk supplier, 2.25g 15.6mmol) and 4-fluorobenzoic acid (2.62g 18.7mmol) are treated with polyphosphoric acid (56.4g) at 150°C for 6h. The reaction mixture is poured on ice-water/NH₃conc. and extracted with ethyl acetate three times. The combined organic phases are dried over Na₂SO₄, filtered and evaporated to dryness to yield the crude product, which is purified by recrystallisation from ethyl acetate/tert.butyl methyl ether to yield the title compound (1.8g 44%) as grey crystals.

¹H-NMR (400MHz; DMSO-d₆): 7.32 (d, 1H); 7.47 (t, 2H); 8.08 (bd, 1H); 8.28 (q, 2H); 13.6 (s, 1H).

MS (m/z) ESI: 247 (MH⁺; 100).

b) 5-Chloro-2-(4-fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)imidazo[4,5-b]pyridine



KN(TMS)₂ (1.42g 7.16mmol) in toluene (7ml) is added at 0°C to a solution of 5-Chloro-2-(4-fluorophenyl)imidazo[4,5-b]pyridine (1.9g 6.66mmol) in DMF (25ml). After stirring 1h at room temperature, 2-methylthio-4-iodopyrimidine (1.8g 7.1mmol) in toluene (7ml) is added dropwise

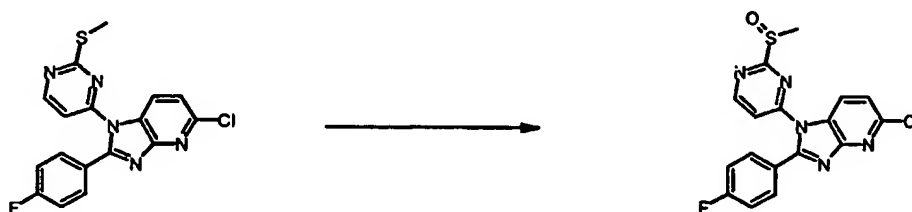
and heated for 20h at 120°C. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na₂SO₄, filtered and evaporated to dryness to yield the crystalline crude product, which after recrystallisation from ethyl acetate yields the title compound as colorless crystals (1.76g 67%).

¹H-NMR (400MHz; CDCl₃): 2.58 (s, 3H); 6.57 (d, 1H); 7.18 (t, 2H); 7.36 (d, 1H); 7.68 (q, 2H); 8.17 (d, 1H); 8.53 (d, 1H)

MS (m/z) ESI: 372 (MH⁺, 100); 352 (10); 336 (20).

The correct regiochemistry is demonstrated 2 steps later on the cyclopentylamine (d) analogue by ROESY.

c) 5-Chloro-2-(4-fluorophenyl)-1-(2-methylsulfinyl-4-pyrimidinyl)imidazo[4,5-b]pyridine

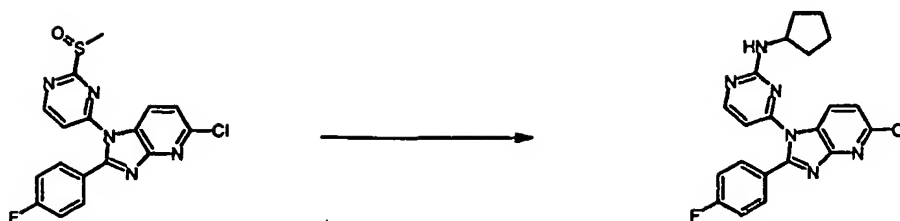


5-Chloro-2-(4-fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)imidazo[4,5-b]pyridine (372mg 1mmol) is dissolved in CH₂Cl₂/HOAc (7ml 5/2) and treated with mCPBA (270mg 70% 1.1mmol) at 0°C for 30min. The reaction mixture is poured on 2N Na₂CO₃ and extracted with ethyl acetate three times. The combined organic phases are dried over Na₂SO₄, filtered, evaporated to dryness and purified by SiO₂ chromatography (ethyl acetate) to yield the title compound (400mg 100%) as yellow foam.

¹H-NMR (400MHz; CDCl₃): 3.08 (s, 3H); 6.92 (d, 1H); 7.25 (t, 2H); 7.42 (d, 1H); 7.68 (q, 2H); 8.55 (d, 1H); 8.78 (bs, 1H).

MS (m/z) ESI: 388 (MH⁺, 100); 352 (30).

d) 5-Chloro-2-(4-fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)imidazo[4,5-b]pyridine

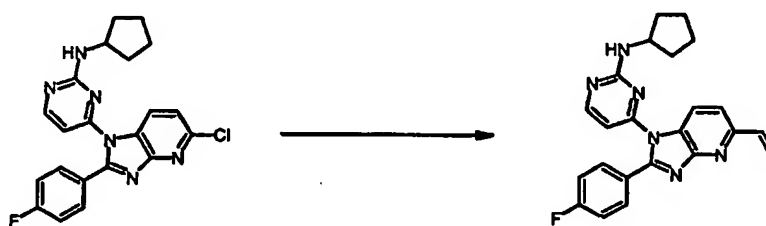


5-Chloro-2-(4-fluorophenyl)-1-(2-methylsulfinyl-4-pyrimidinyl)imidazo[4,5-b]pyridine (200mg 0.52mmol) and cyclopentylamine (1ml) are heated to 80°C for 1h, evaporated and purified by SiO₂ chromatography (acetone/cyclohexane 10/90 to 20/80) to yield the title compound as white crystals (50mg 24%).

¹H-NMR (400MHz; CDCl₃): 1.43-1.86 (m, 6H); 1.95-2.20 (bs, 2H); 4.08-4.42 (bs, 1H); 5.30-5.52 (bs, 1H, NH); 6.20 (bs, 1H); 7.17 (t, 2H); 7.33 (d, 1H); 7.71 (q, 2H); 8.10 (d, 1H); 8.28 (d, 1H). The correct regiochemistry is demonstrated by ROESY.

MS (m/z) ESI: 409 (MH⁺, 100)

e) 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-vinylimidazo[4,5-b]pyridine

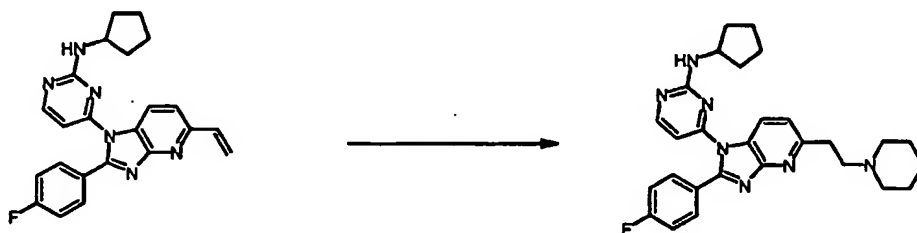


2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-chloroimidazo[4,5-b]pyridine (50mg 0.12mmol), vinyltributylstannane (4.3ml 0.15mmol) and PdCl₂(PPh₃)₂ (8.6mg 0.01mmol) are dissolved in xylene (1ml) and heated to 160°C for 1h under argon. The reaction mixture is purified over SiO₂ (acetone/hexanes 15/85) to yield the title compound as colorless crystals (42mg 86%)

¹H-NMR (400MHz; CDCl₃): 1.45-1.86 (m, 6H); 1.93-2.20 (bs, 2H); 4.06-4.48 (bs, 1H); 5.35 (bs, 1H, NH); 5.53 (d, 1H); 6.21 (bs, 1H); 6.44 (d, 1H); 6.95 (q, 1H); 7.18 (t, 2H); 7.48 (d, 1H); 7.73 (q, 2H); 8.08 (d, 1H); 8.30 (d, 1H).

MS (m/z) ESI: 399 (M-H).

f) 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidino-N-2-ethyl)imidazo-[4,5-b]pyridine

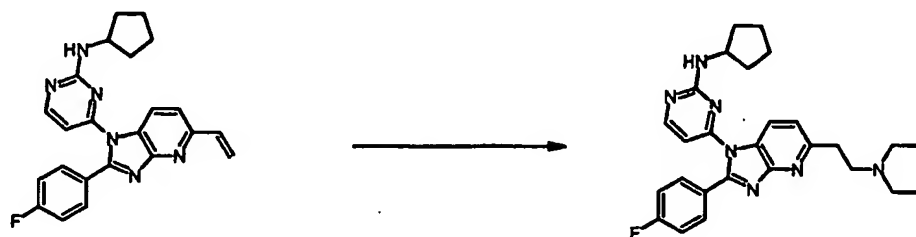


2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-vinylimidazo[4,5-b]pyridine (50mg 0.13mmol) and piperidine (0.3ml 3mmol) are refluxed in HOAc (1ml) for 1.5h, poured on a saturated solution of Na_2CO_3 and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4 , filtered, evaporated to dryness and purified by SiO_2 chromatography (tert.butyl methyl ether/MeOH/ NH_3 conc. 85/15/1) to yield the title compound (60mg 98%) as yellow crystals.

$^1\text{H-NMR}$ (400MHz; DMSO, 120°C): 1.40-1.90 (m, 14H); 2.55 (bs, 2H); 2.75-2.91 (m, 4H); 3.08 (t, 2H); 4.03 (m, 1H); 6.43 (d, 1H); 6.97 (bs, 1H, NH); 7.28 (t, 3H); 7.69 (dd, 2H); 8.00 (d, 1H); 8.38 (d, 1H).

MS (m/z) ESI: 486 (MH^+ ; 100)

Example 6: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(N,N-diethyl-amino-N-2-ethyl)imidazo[4,5-b]pyridine

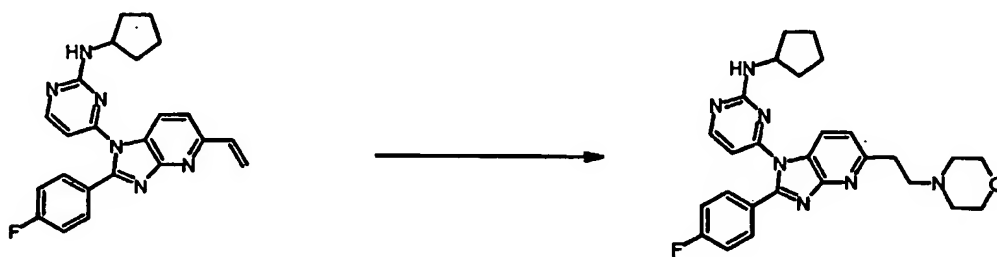


The crystalline title compound (48mg 50%) is prepared by analogy to the previous example.

¹H-NMR (400MHz; CDCl₃): 1.12 (bt, 6H); 1.46-2.20 (m, 8H); 2.71 (bd, 4H); 2.97-3.20 (bd, 4H); 4.05-4.38 (bs, 1H); 5.35 (bs, 1H, NH); 6.18 (bs, 1H); 7.12 (t, 2H); 7.20 (d, 1H); 7.71 (dd, 2H); 8.03 (d, 1H); 8.29 (d, 1H).

MS (m/z) ESI: 474 (MH⁺, 100).

Example 7: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(morpholino-N-2-ethyl)imidazo[4,5-b]pyridine

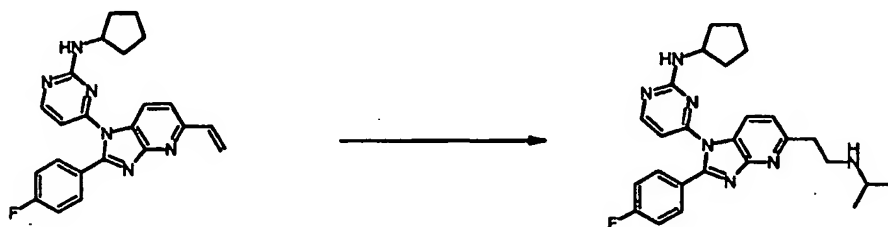


The crystalline title compound (78mg 66%) is prepared by analogy to the previous example.

¹H-NMR (400MHz; CDCl₃): 1.45-1.85 (m, 6H); 1.93-2.13 (bs, 2H); 2.59 (bs, 4H); 2.95 (t, 2H); 3.18 (t, 2H); 3.78 (t, 4H); 4.03-4.41 (bs, 1H); 5.35 (bs, 1H, NH); 6.20 (bs, 1H); 7.15 (t, 2H); 7.20 (d, 1H); 7.72 (dd, 2H); 8.05 (d, 1H); 8.30 (d, 1H).

MS (m/z) ESI: 488 (MH⁺, 100);

Example 8: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(isopropylamino-N-2-ethyl)imidazo[4,5-b]pyridine

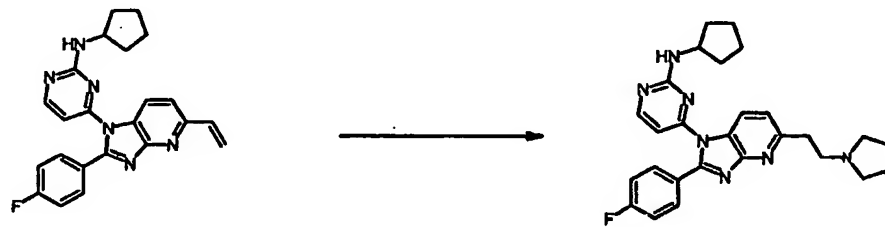


The crystalline title compound (30mg 33%) is prepared by analogy to the previous example.

¹H-NMR (400MHz; CDCl₃): 1.15 (d, 6H); 1.45-2.15 (m, 8H); 2.95 (m, 1H); 3.21 (s, 4H); 4.08-4.35 (bs, 1H); 5.38 (bs, 1H, NH); 6.20 (bs, 1H); 7.16 (t, 2H); 7.22 (d, 1H); 7.73 (dd, 2H); 8.05 (d, 2H); 8.29 (d, 1H).

MS (m/z) ESI: 460 (MH⁺, 100).

Example 9: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(pyrrolidino-N-2-ethyl)imidazo[4,5-b]pyridine

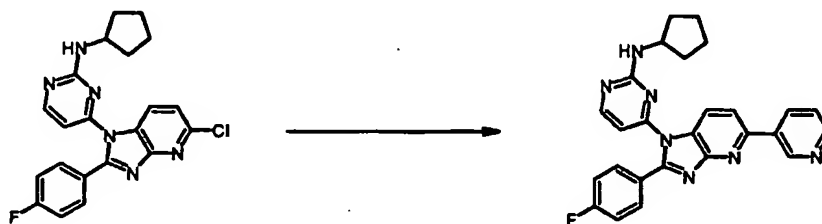


The crystalline title compound (34mg 36%) is prepared by analogy to the previous example.

¹H-NMR (400MHz; CDCl₃): 1.45-2.18 (m, 12H); 2.65 (bs, 4H); 3.03 (m, 2H); 3.23 (m, 2H); 4.20 (bs, 1H); 5.35 (bs 1H, NH); 6.18 (bs, 1H); 7.14 (t, 2H); 7.22 (d, 1H); 7.74 (dd, 2H); 8.04 (d, 1H); 8.28 (d, 1H).

MS (m/z) ESI: 472 (MH⁺, 100).

Example 10: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(3-pyridyl)imidazo-[4,5-b]pyridine

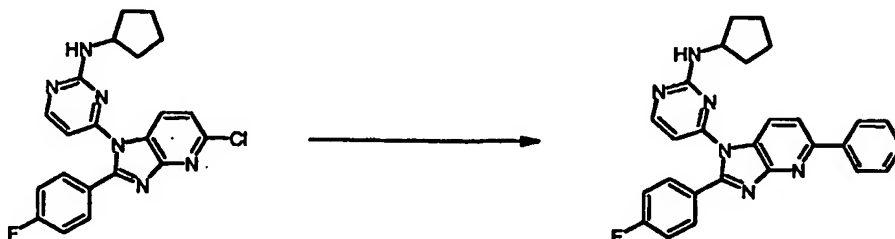


5-Chloro-2-(4-fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)imidazo[4,5-b]pyridine (2g 4.9mmol), 3-tributylstannylpyridine (3.6g 9.8mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (340mg 0.48mmol) are heated in xylene (50ml) for 3h at 150°C under argon. The reaction mixture is filtered at 60°C and chromatographed over SiO_2 (acetone/hexanes 3/7 to 6/4) to yield pale yellow crystals (1.3g). Recrystallisation from THF/hexanes renders the title compound as colorless crystals (985mg 45%).

$^1\text{H-NMR}$ (400MHz; CDCl_3): 1.45-1.90 (m, 6H); 1.95-2.20 (bs, 2H); 4.08-4.45 (bs, 1H); 5.41 (bs, 1H, NH); 6.25 (bs, 1H); 7.18 (t, 2H); 7.48 (m, 1H); 7.78 (dd, 2H); 7.86 (d, 1H); 8.25 (d, 1H); 8.33 (d, 1H); 8.60 (d, 1H); 8.68 (d, 1H); 9.38 (s, 1H).

MS (m/z) ESI: 450 (M-H).

Example 11: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-pyridyl)imidazo[4,5-b]pyridine



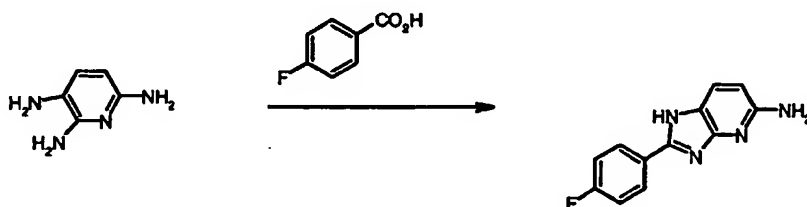
The white crystalline title compound (1.3g 70%) is obtained by analogy to the previous example with the exception that 4-trimethylstannylpyridine was used in the coupling reaction.

¹H-NMR (400MHz; CDCl₃): 1.45-1.90 (m, 6H); 1.95-2.20 (bs, 2H); 4.08-4.45 (bs, 1H); 5.41 (bs, 1H, NH); 6.25 (bs, 1H); 7.18 (t, 2H); 7.78 (dd, 2H); 7.88 (d, 1H); 8.12 (d, 2H); 8.28 (d, 1H); 8.33 (d, 1H); 8.80 (d, 2H).

MS (m/z) ESI: 452.3 (MH⁺, 100).

Example 12: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine

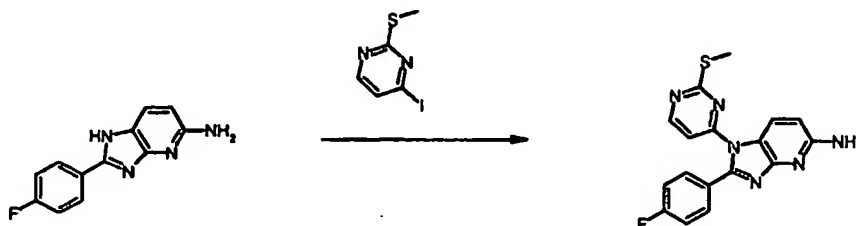
a) 2-(4-Fluorophenyl)-5-aminoimidazo[4,5-b]pyridine



2,3,6-Triaminopyridine (Austin Products; 372mg 3mmol) and 4-fluorobenzoic acid (420mg 3mmol) are treated with polyphosphoric acid (30g) at 150°C for 1h. The reaction mixture is poured on ice-water/NH₃conc. and extracted with ethyl acetate three times. The combined organic phases are dried over Na₂SO₄, filtered and evaporated to dryness to yield the crude product, which is purified by SiO₂ chromatography (acetone/cyclohexane 20/80 to 50/80) and rendered the title compound as pale yellow crystals (200mg 29%)

¹H-NMR (400MHz; DMSO): 5.92 (bs, 2H, NH₂); 6.40 (d, 1H); 7.35 (t, 2H); 7.65 (d, 1H); 8.13 (dd, 2H); 12.80 (bs, 1H, NH).

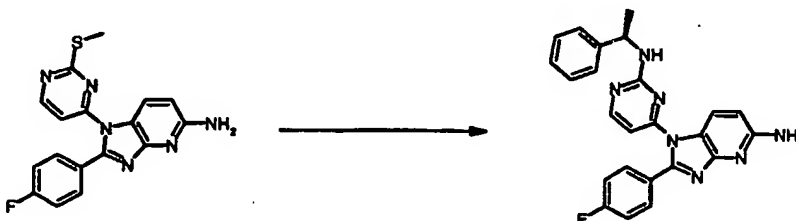
MS (m/z) ESI: 229 (MH⁺, 100).

b) 2-(4-Fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine

KN(TMS)₂ (688mg 3.65mmol) in toluene (3.5ml) is added at 0°C to a solution of 2-(4-fluorophenyl)-5-aminoimidazo[4,5-b]pyridine (684mg 3mmol) in DMF (10ml). After stirring 1h at room temperature, 2-methylthio-4-iodopyrimidine (832mg 3.3mmol) in toluene (3.3ml) is added dropwise and heated for 18h at 120°C. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na₂SO₄, filtered and evaporated to dryness to yield the crude product, which is purified by SiO₂ chromatography (acetone/cyclohexane 20/80 to 60/40) and renders the title compound as a yellow foam (300mg 27%)

¹H-NMR (400MHz; CDCl₃): 2.58 (s, 3H); 4.60 (bs, 2H, NH₂); 6.55 (d, 1H); 6.59 (d, 1H); 7.16 (t, 2H); 7.63 (dd, 2H); 8.00 (d, 1H); 8.48 (d, 1H). The correct regiochemistry was demonstrated by ROESY.

MS (m/z) ESI: 353 (MH⁺, 100).

c) 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine

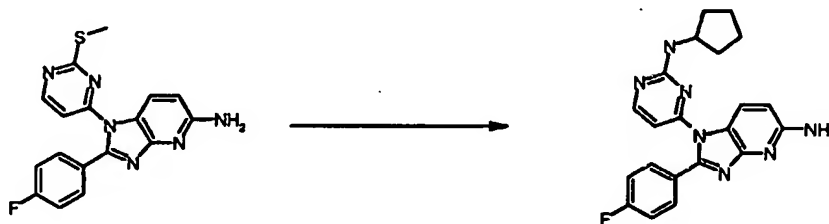
2-(4-Fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine (110mg, 0.31mmol) is dissolved in CH₂Cl₂/HOAc 1:1 (6.2ml), combined at 0°C with mCPBA (84mg 70%, 0.34mmol) and stirred for 30min. The reaction mixture is poured on 2N Na₂CO₃ and extracted

with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4 , filtered and evaporated to dryness to yield the crude sulfoxide (110mg). 50mg are dissolved in 1-(S)-phenylethylamine (0.5ml) and heated to 120°C for 1h. Purification over RP18 ($\text{CH}_3\text{CN}/\text{Water}$ 70/30 to 10/90) yielded the title compound as light brown foam (30mg 52%)

$^1\text{H-NMR}$ (400MHz; CDCl_3): 1.60 (d, 3H); 4.50 (bs, 2H, NH_2); 5.10 (bs, 1H); 5.78 (bs, 1H); 6.08 (d, 1H); 6.25 (bs, 1H); 7.11 (t, 2H); 7.37 (m, 1H); 7.41 (m, 5H); 7.63 (dd, 2H); 8.22 (d, 1H).

MS (m/z) EI: 425 (M^+ , 70); 410 (40).

Example 13: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine



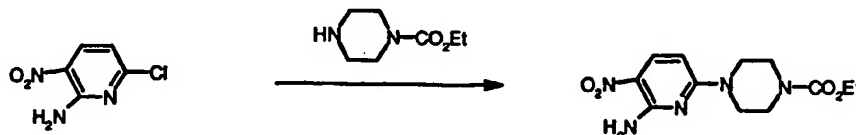
The title compound is prepared from the sulfoxide (60mg 0.16mmol) in the above procedure and cyclopentylamine (0.8ml) by heating to 120°C for 1h and purifying over RP18 ($\text{CH}_3\text{CN}/\text{Water}$ 70/30 to 10/90). The title compound is obtained as a yellow powder (30mg 44%)

$^1\text{H-NMR}$ (400MHz; CDCl_3): 1.47-2.15 (m, 8H); 4.20 (bs, 1H); 4.55 (s, 2H; NH_2); 5.34 (bs, 1H); 6.15 (s, 1H, NH); 6.54 (d, 1H); 7.12 (t, 2H); 7.68 (dd, 2H); 7.93 (d, 1H); 8.25 (d, 1H).

MS (m/z) EI: 389 (M^+ , 100).

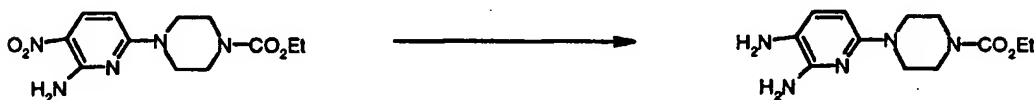
Example 14: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine

a) 5-Nitro-6-amino-2-(4-ethoxycarbonyl-1-piperazinyl)pyridine



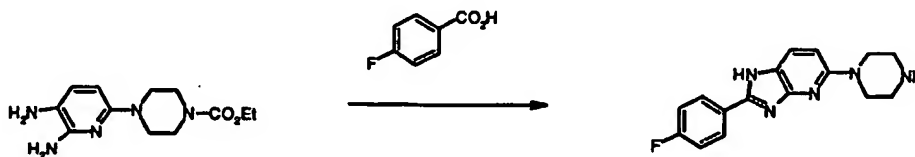
6-Amino-2-chloro-5-nitropyridine (Acros, 3.66g 21mmol) and 1-ethoxycarbonylpiperazine (6.36g 42mmol) in isopropanol (85ml) are refluxed for 3h. The reaction mixture with a yellow precipitate is poured on water/ Na_2CO_3 and extracted twice with methylene chloride. The combined organic phases are dried over Na_2SO_4 , filtered and evaporated to dryness to yield the title compound as yellow crystals, which are purified by recrystallisation from tert.-butyl methyl ether (5.5g 89%). $^1\text{H-NMR}$ (400MHz; CDCl_3): 1.23 (t, 3H); 3.51 (m, 4H); 3.66 (m, 4H); 4.12 (q, 2H); 6.00 (d, 1H); 8.15 (d, 1H). MS (m/z) EI: 295 (M^+ , 60); 193 (50); 167 (100).

b) 5,6-Diamino-2-(4-ethoxycarbonyl-1-piperazinyl)pyridine



5-Nitro-6-amino-2-(4-ethoxycarbonyl-1-piperazinyl)pyridine (4.5g 15.2mmol) in EtOH (200ml) is hydrogenated at 1 atm over 10% Pd/C (1.5g), filtered after hydrogen uptake was complete (2.5h), combined with 4-fluorobenzoic acid (2.13g 15.2mmol) in EtOH (50ml), evaporated to dryness and used without further purification in the following step.

c) 2-(4-Fluorophenyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine



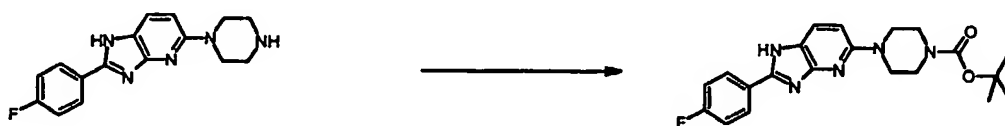
The mixture of 5,6-Diamino-2-(4-ethoxycarbonyl-1-piperazinyl)pyridine from the previous hydrogenation (4.5g, 15.2mmol) and 4-fluorobenzoic acid (2.13g 15.2mmol) is treated with polyphosphoric acid (76g) at 150°C for 1h 15min. The reaction mixture is poured on ice-water/ Na_2CO_3 and extracted with ethyl acetate three times. The combined organic phases are

dried over Na_2SO_4 , filtered and evaporated to dryness to yield the title compound as brownish crystals (1.6g, 35%).

$^1\text{H-NMR}$ (400MHz; DMSO): 2.73 (m, 4H); 3.43 (m, 4H); 6.78 (d, 1H); 7.35 (t, 2H); 7.80 (d, 1H); 8.18 (dd, 2H).

MS (m/z) CI: 298 (MH^+ , 100); 278 (20).

d) 2-(4-Fluorophenyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl)imidazo[4,5-b]pyridine



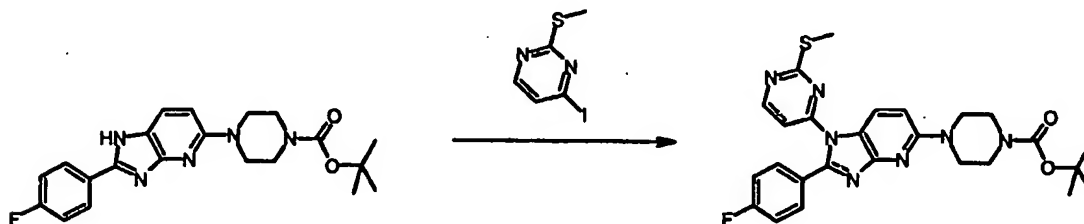
2-(4-Fluorophenyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine (1.57g, 5.3mmol) in THF (53ml) is treated with $(\text{BOC})_2\text{O}$ (1.27g, 5.83mmol) for 30min. at room temperature, poured on water and extracted with ethyl acetate three times. The combined organic phases are washed with brine, dried over Na_2SO_4 , filtered and evaporated to dryness. Purification over SiO_2

(acetone/hexanes 10/80 to 50/50) yields the title compound (1.6g, 74.5%) as brownish crystals.

$^1\text{H-NMR}$ (400MHz; CDCl_3): 1.52 (s, 9H); 3.52-3.73 (bs, 8H); 6.71 (d, 1H); 7.18 (t, 2H); 7.93 (bs, 1H); 8.07 (bt, 2H), 10.70 (bs, 1H, NH).

MS (m/z) EI: 397 (M^+ , 100); 341 (90); 241 (100).

e) 2-(4-Fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl) imidazo[4,5-b]pyridine



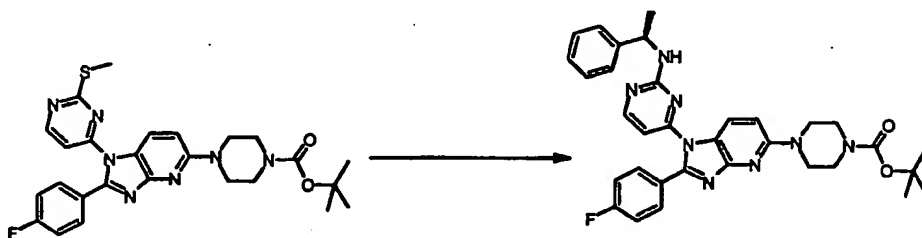
$\text{KN}(\text{TMS})_2$ (812mg, 3.85mmol) in toluene (3.85ml) is added at 0°C to a solution of 2-(4-Fluorophenyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl)imidazo[4,5-b]pyridine (1.4g, 3.5mmol) in DMF (7ml). After stirring at room temperature for 30min., 4-iodo-2-methylthiopyrimidine

(970mg, 3.85mmol) in toluene (3.85ml) is added and the reaction stirred at room temperature for 1h. Toluene is evaporated, the reaction mixture heated to 120°C for 18h, poured on water and extracted with ethyl acetate (containing 5% EtOH) three times. The combined organic phases are washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. Purification over SiO₂ (acetone/hexanes 20/80) renders the title compound (950mg, 52%) as colorless foam.

¹H-NMR (400MHz; CDCl₃): 1.51 (s, 9H); 2.55 (s, 3H); 3.61 (m, 4H); 3.69 (m, 4H); 6.55 (d, 1H); 6.77 (d, 1H); 7.15 (t, 2H); 7.65 (dd, 2H); 8.06 (d, 1H); 8.47 (d, 1H). The correct regiochemistry was demonstrated by ROESY.

MS (m/z) ESI: 522 (MH⁺, 100).

f) 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl)imidazo[4,5-b]pyridine

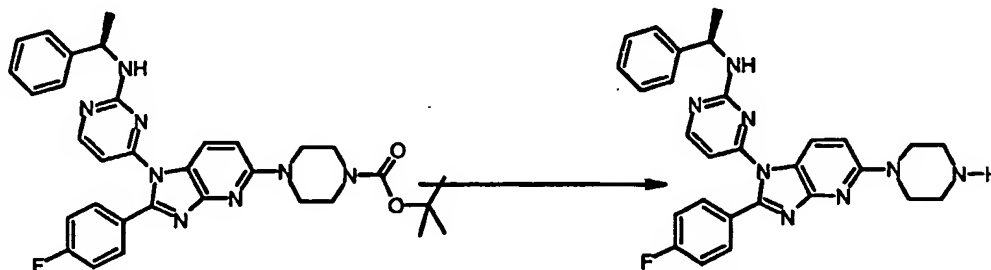


2-(4-Fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl)imidazo[4,5-b]pyridine (106mg, 0.2mmol) is dissolved in CH₂Cl₂/HOAc 1:1 (10ml), combined with mCPBA (113mg 70%, 0.24mmol) and stirred for 15min. The reaction mixture is poured on water and extracted with CH₂Cl₂ three times. The combined organic phases are dried over Na₂SO₄, filtered and evaporated to dryness to yield the crude sulfoxide (100mg), which is dissolved in 1-(S)-phenylethylamine (0.2ml) and heated to 120°C for 1h. Purification over SiO₂ (acetone/hexanes 1:1) yielded the title compound as colorless foam (45mg 35%)

¹H-NMR (400MHz; CDCl₃): 1.51 (s, 9H); 1.62 (d, 3H); 3.58-3.67 (m, 8H); 5.10 (bs, 1H); 5.75 (bs, 1H); 6.08 (d, 1H); 6.45 (bs 1H, NH); 7.11 (t, 2H); 7.33-7.43 (m, 6H); 7.65 (dd, 2H); 8.22 (d, 1H).

MS (m/z) ESI: 595 (MH⁺, 100).

g) 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine



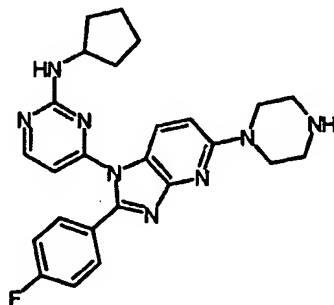
2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl)imidazo[4,5-b]pyridine (280mg, 0.67mmol) is dissolved in EtOH/HClconc 1/1 (9.4ml) and stirred at room temperature for 30min. The reaction mixture is poured on a saturated solution of Na₂CO₃ and extracted with ethyl acetate three times. The combined organic phases are dried over Na₂SO₄, filtered and evaporated to dryness. Purification over SiO₂ (tert.-butyl methyl ether/MeOH/NH₃conc 90/9/1) yields the title compound as a yellow foam (200mg, 86%)

¹H-NMR (400MHz; CDCl₃): 1.61 (d, 3H); 1.89 (bs, 1H); 3.06 (bt, 4H); 3.62 (bt, 4H); 5.10 (bs, 1H); 5.75 (bs, 1H); 6.09 (d, 1H); 6.45 (bs, 1H); 7.05 (bs, 1H); 7.11 (t, 2H); 7.32-7.46 (m, 5H); 7.66 (dd, 2H); 8.21 (d, 1H).

MS (m/z) ESI: 495 (MH⁺, 100).

The compounds of Examples 15-17 are similarly prepared:

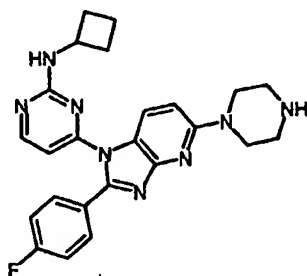
Example 15: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine:



¹H-NMR (400MHz; DMSO-d₆, 120^o C): 1.43-1.58 (m, 4H); 1.65-1.75 (m, 2H); 1.80-1.90 (m, 2H); 3.10 (t, 4H); 3.73 (t, 4H); 4.00-4.08 (m, 1H); 6.38 (d, 1H); 6.90 (d, 1H); 6.95 (bd, 1H, NH); 7.26 (t, 2H); 7.68 (dd, 2H); 7.96 (d, 1H); 8.34 (d, 1H).

MS (m/z) ESI: 459.3 (MH⁺, 100).

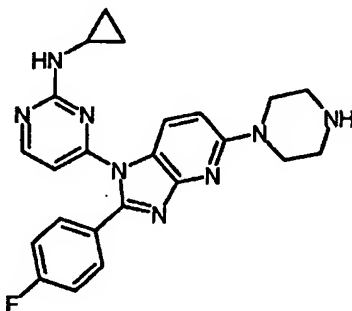
Example 16: 2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine:



¹H-NMR (400MHz; CDCl₃): 1.65-1.89 (m, 4H); 1.91-2.05 (m, 2H); 2.43 (bs, 1H); 3.06 (t, 4H); 3.67 (t, 4H); 4.40 (bs, 1H, NH); 5.50 (bd, 1H, NH); 6.17 (bd, 1H); 6.75 (d, 1H); 7.11 (t, 2H); 7.68 (dd, 2H); 7.97 (d, 1H); 8.23 (d, 1H).

MS (m/z) ESI: 445.3 (MH⁺, 100).

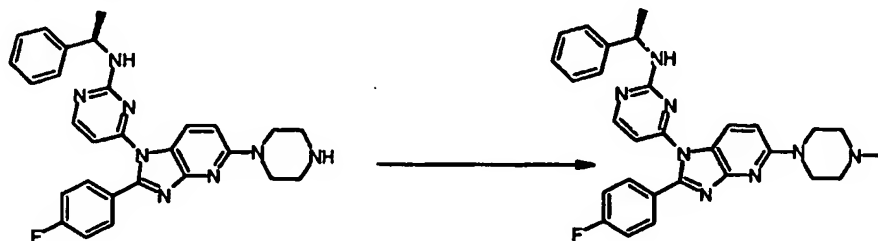
Example 17: 2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine:



¹H-NMR (400MHz; DMSO-d₆): 0.47 (bs, 2H); 0.62 (bs, 2H); 2.33 (bs, 1H); 2.83 (bt, 4H); 3.47 (bt, 4H); 6.34 (bs, 1H); 6.92 (d, 1H, NH); 7.36 (t, 2H); 7.65 (dd, 2H); 7.85 (bd, 1H); 8.10 (bs, 1H); 8.36 (bd, 1H).

MS (m/z) ESI: 431.2 (MH⁺, 100).

Example 18: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl) imidazo[4,5-b]pyridine



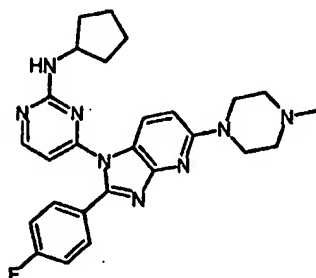
2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl) imidazo[4,5-b]pyridine (50mg, 0.1mmol) is dissolved in MeOH (2.5ml). An aqueous 36%-solution of formaldehyde (15.8ml, 0.2mmol) is added and stirred for 30min. NaBH₄ (7.5mg, 0.2mmol) is added and stirring continued for 30min. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na₂SO₄, filtered and evaporated to dryness. Purification over SiO₂ (tert.-butyl methyl ether/MeOH/NH₃conc 90/9/1) yields the title compound as a yellow powder (35mg 68%)

¹H-NMR (400MHz; CDCl₃): 1.61 (d, 3H); 2.40 (s, 3H); 2.60 (bt, 4H); 3.68 (bt, 4H); 5.12 (m, 1H); 5.76 (bs, 1H, NH); 6.08 (d, 1H); 6.48 (bs 1H); 7.10 (t, 2H); 7.35-7.46 (m, 6H); 7.66 (dd, 2H); 8.21 (d, 1H).

MS (m/z) ESI: 509 (MH⁺, 100).

The compounds of Examples 19-21 are similarly prepared:

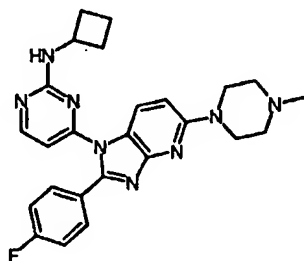
Example 19: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine:



¹H-NMR (400MHz; DMSO-d₆): 1.45-1.58 (m, 2H); 1.61-1.83 (m, 4H); 1.97-2.13 (m, 2H); 2.38 (s, 3H); 2.59 (t, 4H); 3.71 (t, 4H); 4.10-4.31 (m, 1H); 5.33 (bd, 1H, NH); 6.16 (bs, 1H); 6.75 (d, 1H); 7.11 (t, 2H); 7.68 (dd, 2H); 7.97 (d, 1H); 8.23 (d, 1H).

MS (m/z) ESI: 473.3 (MH⁺, 100).

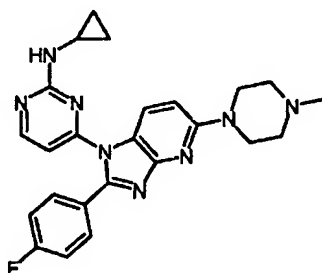
Example 20: 2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine:



¹H-NMR (400MHz; DMSO-d₆): 1.45-2.12 (m, 6H); 2.20 (m, 1H); 2.25 (s, 3H); 2.45 (bt, 4H); 3.55 (bt, 4H); 6.95 (bs, 1H); 7.32 (t, 2H); 7.62 (bs, 2H); 7.93 (bd, 2H); 8.33 (bs, 1H).

MS (m/z) ESI: 459.3 (MH⁺, 100).

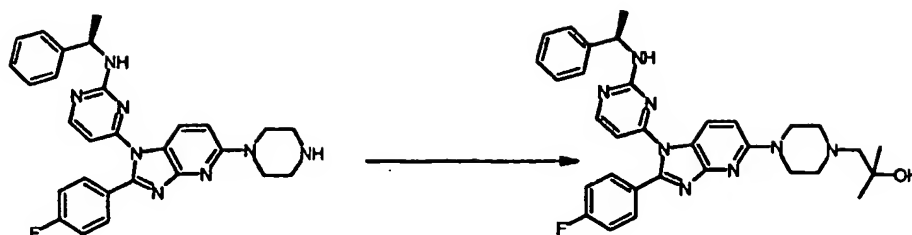
Example 21: 2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine:



¹H-NMR (400MHz; CDCl₃): 0.64 (m, 2H); 0.88 (m, 2H); 2.38 (s, 3H); 2.58 (t, 4H); 2.82 (bs, 1H); 3.72 (t, 4H); 5.58 (s, 1H, NH); 6.19 (d, 1H); 6.74 (d, 1H); 7.13 (t, 2H); 7.71 (dd, 2H); 8.12 (bs, 1H); 8.28 (bs, 1H).

MS (m/z) ESI: 445 (MH⁺, 100).

Example 22: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine



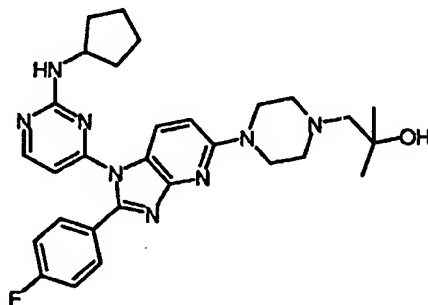
2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine (60mg, 0.12 mmol) and isobutyleneoxide (43.5ml 0.6mmol) in EtOH (6ml) are heated at 80°C for 3h. The reaction mixture is evaporated and purified by SiO₂ chromatography (tert.-butyl methyl ether/MeOH/NH₃conc. 97/2.7/0.3) to yield the title compound as a yellow foam (40mg 60%).

¹H-NMR (400MHz; DMSO, 120°C): 1.18 (s, 6H); 1.48 (d, 3H); 2.43 (s, 2H); 2.72 (dd, 4H); 3.58 (dd, 4H); 5.10 (m, 1H); 6.32 (d, 1H); 6.73 (d, 1H); 7.21 (t, 2H); 7.28-7.38 (m, 5H); 7.43 (bd, 1H, NH); 7.62 (dd, 2H); 7.65 (d, 1H); 8.32 (d, 1H).

MS (m/z) ESI: 567 (MH⁺, 100).

The compounds of Examples 23-25 are similarly prepared:

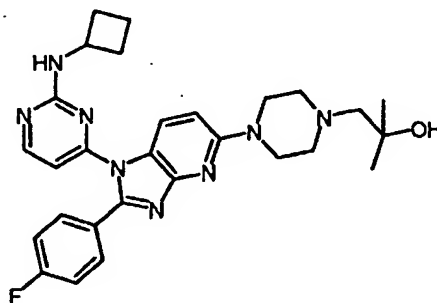
Example 23: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine



¹H-NMR (400MHz; DMSO): 1.24 (s, 6H); 1.52 (bs, 2H); 1.67 (bs, 2H); 1.79 (bs, 2H); 2.08 (bs, 2H); 2.42 (s, 2H); 2.82 (bt, 4H); 3.20 (bs, 1H, OH); 3.70 (bt, 4H); 4.22 (bs, 1H); 5.35 (bd, 1H, NH); 6.17 (bs, 1H); 6.74 (d, 1H); 7.12 (t, 2H); 7.70 (dd, 2H); 7.97 (d, 1H); 8.23 (d, 1H).

MS (m/z) ESI: 531.3 (MH⁺, 100).

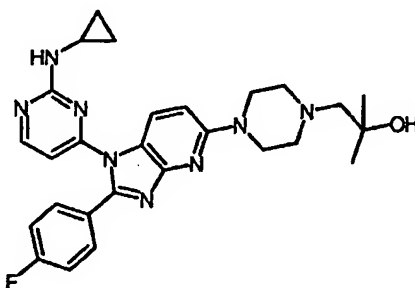
Example 24: 2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine



¹H-NMR (400MHz; DMSO): 1.25 (s, 6H); 1.56-2.03 (m, 6H); 2.43 (s, 2H); 2.82 (t, 4H); 3.15 (bs, 1H, OH); 3.70 (t, 4H); 4.40 (bs, 1H, NH); 5.50 (bd, 1H, NH); 6.15 (bs, 1H); 6.74 (d, 1H); 7.12 (t, 2H); 7.69 (dd, 2H); 7.98 (d, 1H); 8.25 (d, 1H).

MS (m/z) ESI: 517.4 (MH⁺, 35).

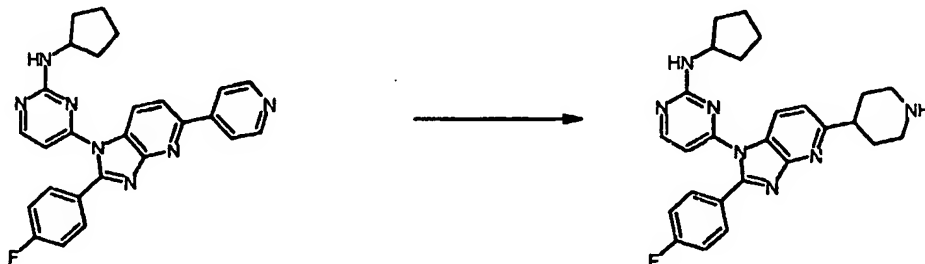
Example 25: 2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine



¹H-NMR (400MHz; DMSO): 0.64 (m, 2H); 0.88 (m, 2H); 1.25 (s, 6H); 2.42 (s, 2H); 2.83 (m, 5H); 3.17 (s, 1H, OH); 3.70 (bt, 4H); 5.57 (s, 1H, NH); 6.20 (d, 1H); 6.73 (d, 1H); 7.13 (t, 2H); 7.71 (dd, 2H); 8.12 (bs, 1H); 8.29 (bs, 1H).

MS (m/z) ESI: 503.3 (MH⁺, 40).

Example 26: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-piperidinyl)imidazo[4,5-b]pyridine

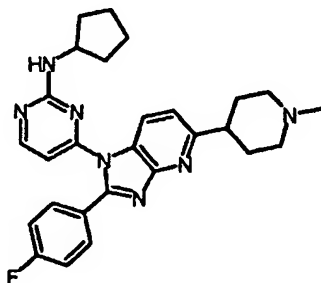


2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-pyridinyl)imidazo[4,5-b]pyridine (example 7; 100mg; 0.22mmol) is dissolved in HOAc (120ml) and hydrogenated over Pd/C (10%, 200mg) in a Parr apparatus for 48h at room temperature. The reaction mixture is filtered and evaporated to dryness delivering the title compound as yellow crystals, which are recrystallised from MeOH and gave the title compound as colorless crystals (70mg; 65%).

¹H-NMR (400MHz; DMSO-d₆, 120°C): 1.49 (m, 4H); 1.68 (m, 2H); 1.83 (m, 2H); 2.10 (m, 4H); 3.05 (dt, 4H); 3.18 (m, 1H); 3.48 (m, 4H); 4.03 (m, 1H); 6.45 (d, 1H); 7.05 (bd, 1H, NH); 7.30 (m, 2H); 7.70 (m, 2H); 8.08 (d, 1H); 8.40 (d, 1H).

MS (m/z) ESI: 458.3 (MH⁺; 100).

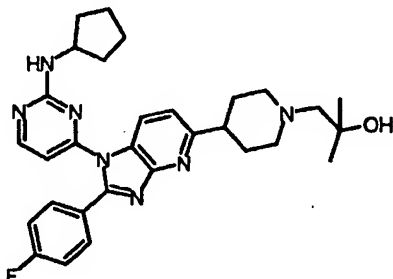
Example 27: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-methyl-4-piperidinyl)imidazo[4,5-b]pyridine



The title compound is prepared in analogy to Example 18.

MS (m/z) ESI: 472.4 (MH⁺, 100).

Example 28: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-(2-hydroxy-2-methyl)propyl-4-piperidiny)imidazo[4,5-b]pyridine

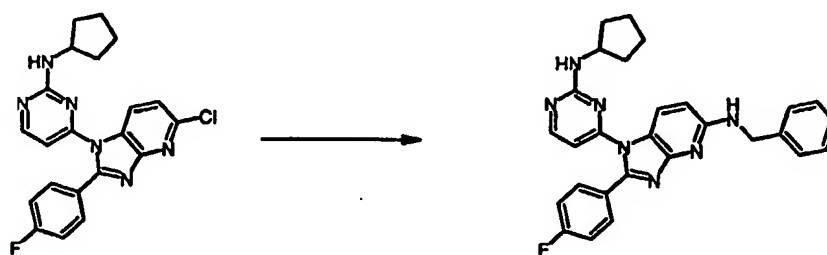


The title compound is prepared in analogy to Example 22.

¹H-NMR (400MHz; DMSO-d₆, 120°C): 1.21 (s, 6H); 1.43-1.83 (m, 8H); 1.95-2.18 (m, 5H); 2.41 (s, 2H); 2.56 (bt, 2H); 2.88 (bt, 1H); 3.08 (bd, 2H); 5.37 (bs, 1H, NH); 6.21 (bs, 1H); 7.13 (t, 2H); 7.21 (d, 1H); 7.72 (dd, 2H); 8.06 (d, 1H); 8.28 (d, 1H).

MS (m/z) ESI: 530 (MH⁺, 100)

Example 29: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(benzylamino)imidazo[4,5-b]pyridine

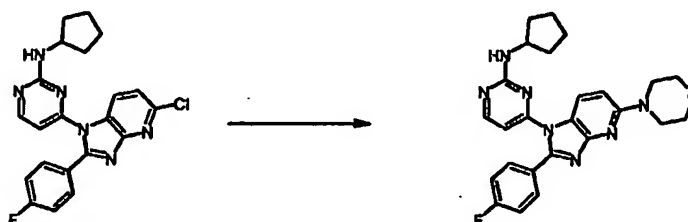


2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(chloro)imidazo[4,5-b]pyridine (100mg; 0.25mmol), R-(+)-BINAP (10mg; 0.016mmol), Pd₂(dba)₃ (22mg; 0.024mmol) are suspended in xylene (16ml), benzylamine (0.53ml; 4.9mmol) is added, followed by NaOtBu (47mg; 0.49mmol) and heated to 160°C for 10 min. under argon. The reaction mixture is poured on water (100ml) containing HOAc (2ml) and extracted with TBME three times. The combined organic phases are washed with 2N Na₂CO₃, dried over Na₂SO₄ and evaporated to dryness. Purification via SiO₂ chromatography (TBME/hexane 6:4 to 10:0) and recrystallisation from TBME yields the title compound as colorless crystals (50mg; 50%).

¹H-NMR (400MHz; CDCl₃): 1.45-1.85 (m, 6H); 1.95-2.13 (m, 2H); 4.25 (bs, 1H); 4.72 (d, 1H);

4.86 (bt, 1H, NH); 5.31 (bd, 1H, NH); 6.15 (, bs, 1H); 6.43 (d, 1H); 7.11 (t, 2H); 7.28 (m, 3H); 7.35 (t, 2H); 7.45 (d, 1H); 7.68 (dd, 2H); 7.89 (d, 1H); 8.23 (d, 1H).
MS (m/z) ESI: 480 (MH⁺, 100).

Example 30: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(morpholino)imidazo[4,5-b]pyridine



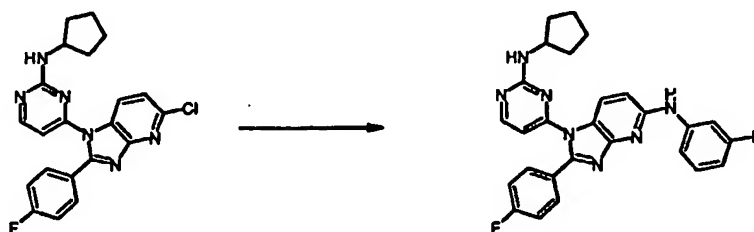
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(chloro)imidazo[4,5-b]pyridine (100mg; 0.25mmol), R-(+)-BINAP (10mg; 0.016mmol), Pd₂(dba)₃ (22mg; 0.024mmol) are suspended in xylene (16ml), morpholine (0.43ml; 4.9mmol) is added, followed by NaOtBu (47mg; 0.49mmol) and heated to 160°C for 10 min. under argon. The reaction mixture is poured on water (100ml) containing HOAc (2ml) and extracted with TBME three times. The combined organic phases are washed with 2N Na₂CO₃, dried over Na₂SO₄ and evaporated to dryness. Purification via SiO₂ chromatography (TBME/hexane 7:3 to 10:0) and recrystallisation from TBME yields the title compound as colorless crystals (22mg; 19%).

¹H-NMR (400MHz; CDCl₃): 1.47-1.84 (m, 6H); 1.97-2.17 (bs, 2H); 3.65 (m, 4H); 3.88 (m, 4H); 4.22 (bs, 1H); 5.33 (bs, 1H, NH); 6.16 (bs, 1H); 6.72 (d, 1H); 7.11 (t, 2H); 7.69 (dd, 2H); 8.00 (d, 1H); 8.25 (bd, 1H).

MS (m/z) ESI: 460 (MH⁺, 100).

Example 31: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(3-fluorophenylamino)imidazo[4,5-b]pyridine

The title compound is prepared in analogy to Example 29

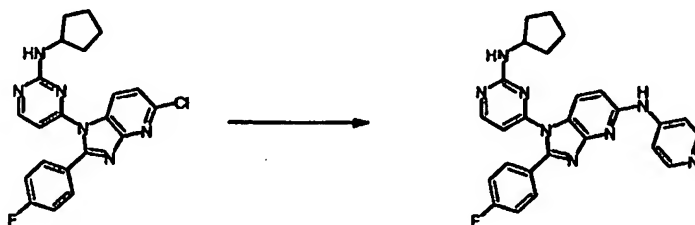


¹H-NMR (400MHz, CDCl₃): 1.48-1.87 (m, 6H); 1.95-2.18 (m, 2H); 4.22 (s, 1H); 5.37 (bs, 1H, NH); 6.15 (bs, 1H); 6.72 (bs, 2H); 6.86 (d, 1H); 7.15 (t, 2H); 7.28 (m, 2H); 7.53 (d, 1H); 7.70 (dd, 2H); 8.03 (d, 1H); 8.27 (d, 1H).

MS (m/z) ESI: 484 (MH⁺, 100).

Example 32: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(pyridyl-4-amino)imidazo[4,5-b]pyridine

The title compound is prepared in analogy to Example 29.

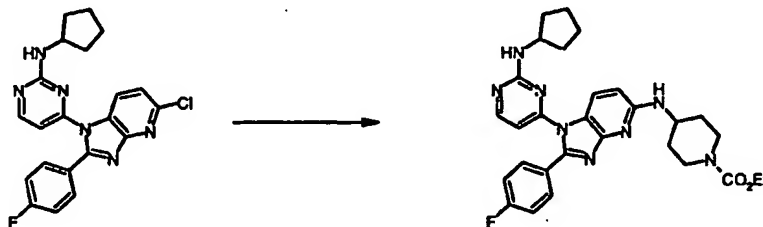


¹H-NMR (400MHz, CDCl₃): 1.47-1.93 (m, 6H); 1.97-2.20 (m, 2H); 4.22 (m, 1H); 5.40 (d, 1H, NH); 6.17 (bs, 1H); 6.93 (d, 1H); 7.18 (m, 2H); 7.71 (m, 4H); 8.12 (d, 1H); 8.28 (d, 1H); 8.42 (d, 2H).

MS (m/z) ESI: 467 (MH⁺, 100).

Example 33: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-ethoxycarbonyl piperidine-4-amino)imidazo[4,5-b]pyridine

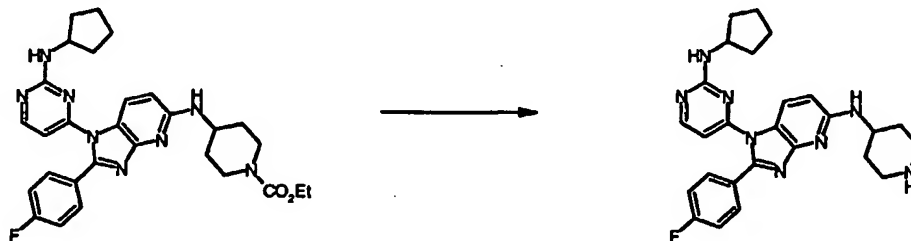
The title compound is prepared in analogy to Example 29



¹H-NMR (400MHz, CDCl₃): 1.31 (t, 3H); 1.38-1.85 (m, 10H); 1.93-2.13 (bs, 1H); 2.21 (bd, 2H); 3.05 (bt, 2H); 4.03-4.39 (m, 4H); 5.33 (bs, 1H, NH); 6.15 (bs, 1H); 6.40 (d, 1H); 7.11 (t, 2H); 7.66 (dd, 2H); 7.88 (d, 1H); 8.23 (d, 1H).

MS (m/z) ESI: 545 (MH⁺, 100).

Example 34: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidine-4-amino)imidazo[4,5-b]pyridine



2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-ethoxycarbonylpiperidin-4-amino)imidazo[4,5-b]pyridine (58mg; 0.1mmol) is dissolved in CHCl₃ (2ml) and treated with trimethylsilyliodide (0.3ml; 2.2mmol) in a sealed vessel at 60°C for 5h. 6N HCl in isopropanol is added to the reaction mixture, which is then poured on 2N Na₂CO₃/ 2N NaOH and extracted with CH₂Cl₂ three times. The combined organic phases are dried over Na₂SO₄ and evaporated to dryness to yield the crude title compound, which is purified via recrystallisation from THF/TBME (44mg; 88%).

¹H-NMR (400MHz, CDCl₃): 1.35-1.82 (m, 8H); 2.06 (bs, 2H); 2.22 (bd, 2H); 2.82 (bt, 2H);

3.15 (bd, 2H); 4.06-4.32 (m, 3H); 4.39 (d, 1H, NH); 5.32 (bd, 1H, NH); 6.14 (bs, 1H); 6.38 (d, 1H); 7.10 (t, 2H); 7.66 (dd, 2H); 7.87 (d, 1H); 8.23 (d, 1H).

MS (m/z) ESI: 473.1 (MH⁺, 100).

The Agents of the Invention, as defined above, e.g., of formula I, II and V particularly as exemplified, in free or pharmaceutically acceptable acid addition salt form, exhibit pharmacological activity and are useful as pharmaceuticals, e.g. for therapy, in the treatment of diseases and conditions as hereinafter set forth.

In particular Agents of the Invention possess p38 MAP kinase (Mitogen Activated Protein Kinase) inhibiting activity. Thus the Agents of the Invention act to inhibit production of inflammatory cytokines, such as TNF- α and IL-1, and also to potentially block the effects of these cytokines on their target cells. These and other pharmacological activities of the Agents of the Invention as may be demonstrated in standard test methods for example as described below:

p38 MAP kinase Assay

The substrate (GST-ATF-2; a fusion protein comprising amino acids 1-109 of ATF-2 and the GST protein obtained by expression in *E. coli*) is coated onto the wells of microtiter plates (50 μ l/well; 1 μ g/ml in PBS/0.02% Na azide) overnight at 4 °C. The following day, the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide and are blocked with PBS/2% BSA/0.02% Na Azide for 1 h at 37 °C. Plates are washed again 4 times with PBS/0.5% Tween 20/0.02% Na azide. The kinase cascade reaction is then started by adding the following reactants in 10 μ l aliquots to a final reaction volume of 50 μ l.

1. Agents of the Invention titrated from 10 to 0.001 μ M in 10-fold dilutions or solvent (DMSO) or H₂O.
2. Kinase buffer (5x); pH 7.4; 125 mM Hepes (Stock at 1M; Gibco #15630-056), 125 mM β -glycerophosphate (Sigma #G-6251); 125 mM MgCl₂ (Merck #5833); 0.5 mM Sodium orthovanadate (Sigma #5-6508), 10 mM DTT (Boehringer Mannheim #708992). The (5x) kinase buffer must be prepared fresh the day of the assay from 5x stock solutions kept at RT. DTT is kept at -20 °C and is added as the last reagent.

3. His-p38 MAP kinase (10 ng/well; Novartis - a fusion protein comprising full length murine p38 MAP kinase and a His tag, obtained by expression in *E. coli*)
4. cold ATP (final concentration 120 μ M; Sigma #A-9187)
5. Water

After 1h at 37 °C the kinase reaction is terminated by washing the plates four times as previously described. Phosphorylated GST-ATF-2 is then detected by adding:

1. the PhosphoPlus ATF-2 (Thr71) Antibody (50 μ l/well; 1/1000 final dilution in PBS/2% BSA/0.02% Na Azide; New England Biolabs #9221L) for 90 min at RT.
2. Biotin labelled goat-anti-rabbit IgG (50 μ l/well; 1/3000 final dilution in PBS/2% BSA/0.02% Na Azide; Sigma #B-9642) for 90 min at RT.
3. Streptavidin-alkaline phosphatase (50 μ l/well; 1/5000 dilution in PBS/2% BSA/0.02% Na Azide; Jackson Immunoresearch #016-050-084) for 30 min at RT.
4. Substrate (100 μ l/well; Sigma 104 Phosphatase substrate tablets, 5 mg/tablet; #104-105; 1 mg/ml in substrate buffer, Diethanolamine (97 ml/l; Merck #803116) + $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ (100 mg/l; Merck #5833) + Na Azide (0.2 g/l) + HCl 1M to pH 9.8) 30 min at RT.

After step 1,2 and 3 the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide. After step 4, the plates are read in a Bio-Rad microplate reader in a dual wavelength mode (measurement filter 405 nm and reference filter 490 nm). The background value (without ATP) is subtracted and IC_{50} values are calculated using the Origin computer program (4 parameter logistic function).

Agents of the Invention typically have IC_{50} s for p38 MAP kinase inhibition in the range from about 100 nM to about 5 nM or less when tested in the above assay.

Assay for Inhibition of TNF- α release from hPBMCs

Human peripheral blood mononuclear cells (hPBMCs) are prepared from the peripheral blood of healthy volunteers using ficoll-hypaque density separation according to the method of Hansell et al., *J. Imm. Methods* (1991) 145: 105. and used at a concentration of 10^5 cells/well in RPMI 1640 plus 10% FCS. Cells are incubated with serial dilutions of the test compounds for 30 minutes at 37°C prior to the addition of IFN γ (100 U/ml) and LPS (5 mg/ ml) and subsequently further incubated for three hours. Incubation is terminated by centrifugation at 1400 RPM for 10 min. TNF- α in the supernatant

is measured using a commercial ELISA (Innotest hTNFa, available from Innogenetics N.V., Zwijnaarde, Belgium). Agents of the Invention are tested at concentrations of from 0 to 10 mM. Exemplified Agents of the Invention typically suppress TNF release in this assay with an IC_{50} of from about ? nM to about ? nM or less when tested in this assay.

Assay for Inhibition of TNF- α Production in LPS stimulated mice

Injection of lipopolysaccharide (LPS) induces a rapid release of soluble tumour necrosis factor (TNF- α) into the periphery. This model is be used to analyse prospective blockers of TNF release in vivo.

LPS (20 mg/kg) is injected i.v. into OF1 mice (female, 8 week old). One (1) hour later blood is withdrawn from the animals and TNF levels are analysed in the plasma by an ELISA method using an antibody to TNF- α . Using 20 mg/kg of LPS levels of up to 15 ng of TNF- α / ml plasma are usually induced. Compounds to be evaluated are given either orally or s.c. 1 to 4 hours prior to the LPS injection. Inhibition of LPS-induced TNF-release is taken as the readout.

Agents of the Invention typically inhibit TNF production to the extent of up to about 50% or more in the above assay when administered at 10 mg/kg p.o.

As indicated in the above assays Agents of the Invention are potent inhibitors of TNF- α release. Accordingly, the Novel Compounds have pharmaceutical utility as follows:

Agents of the Invention are useful for the prophylaxis and treatment of diseases or pathological conditions mediated by cytokines such as TNF α and IL-1, e.g., inflammatory conditions, autoimmune diseases, severe infections, and organ or tissue transplant rejection, e.g. for the treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants and for the prevention of graft-versus-host disease, such as following bone marrow transplants.

Agents of the Invention are particularly useful for the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with

an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific auto-immune diseases for which Agents of the Invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Agents of the Invention are also useful for the treatment, prevention, or amelioration of asthma, bronchitis, pneumoconiosis, pulmonary emphysema, and other obstructive or inflammatory diseases of the airways.

Agents of the Invention are useful for treating undesirable acute and hyperacute inflammatory reactions which are mediated by TNF, especially by TNF α , e.g., acute infections, for example septic shock (e.g., endotoxic shock and adult respiratory distress syndrome), meningitis, pneumonia; and severe burns; and for the treatment of cachexia or wasting syndrome associated with morbid TNF release, consequent to infection, cancer, or organ dysfunction, especially AIDS -related cachexia, e.g., associated with or consequential to HIV infection.

Agents of the Invention are also useful for the treatment of neurodegenerative diseases, such as Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis including demyelination and oligodendrocyte loss in multiple sclerosis and inflammatory nervous system diseases, such as neuroinflammatory and stroke.

Agents of the Invention are particularly useful for treating diseases of bone metabolism including osteoarthritis, osteoporosis and other inflammatory arthritides.

For the above indications the appropriate dosage will, of course, vary depending, for example, on the particular Agent of the Invention employed, the subject to be treated, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are obtained at daily dosages of from about 1 to about 10mg/kg/day p.o.. In larger mammals, for example humans, an indicated daily dosage is in the range of from about 50 to about 750mg of an Agent of the Invention administered orally once or, more suitably, in divided dosages two to four times/day.

The Agents of the Invention may be administered by any conventional route, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Normally for systemic administration oral dosage forms are preferred, although for some indications the Agents of the Invention may also be administered topically or dermally, e.g. in the form of a dermal cream or gel or like preparation or, for the purposes of application to the eye, in the form of an ocular cream, gel or eye-drop preparation; or may be administered by inhalation, e.g., for treating asthma. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 250mg of Agent of the Invention per unit dosage.

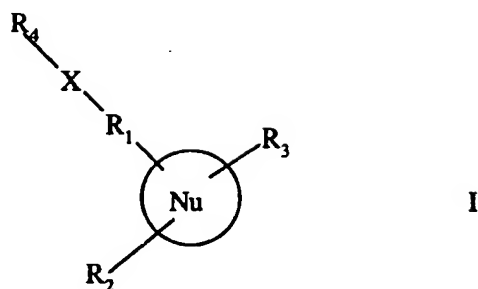
In accordance with the foregoing the present invention also provides in a further series of embodiments:

A. A method of inhibiting production of soluble TNF, especially $\text{TNF}\alpha$, or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of an Agent of the Invention, or a method of treating any of the above mentioned conditions, particularly a method of treating an inflammatory or autoimmune disease or condition, e.g. rheumatoid arthritis, or alleviating one or more symptoms of any of the above mentioned conditions.

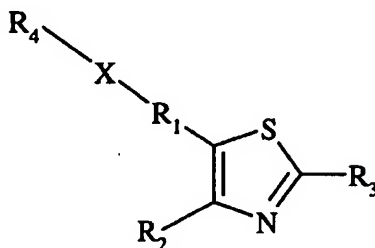
- B. An Agent of the Invention for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.
- C. A pharmaceutical composition comprising an Agent of the Invention in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.
- D. Use of an Agent of the Invention in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune of inflammatory disease or condition.

CLAIMS

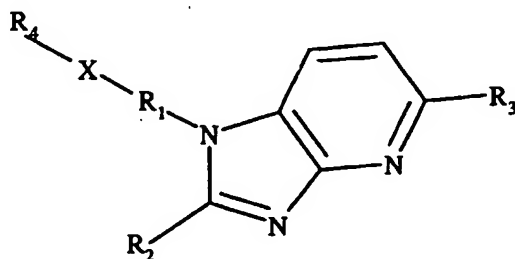
1. A compound of formula I



wherein Nu is a heterocyclic nucleus selected from thiazole in which the R₁, R₂ and R₃ substituents are disposed as indicated below



or imidazo[4,5-b]pyridine in which the R₁, R₂ and R₃ substituents are disposed as indicated below



wherein

R₁ is pyrimidyl or pyridyl;

X is -NR₆-Y-, -O- or -S-,

where R_6 is H, C_1 - C_4 alkyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl- C_1 - C_3 alkyl, C_6 - C_{18} aryl, C_3 - C_{18} heteroaryl, C_7 - C_{19} aralkyl or C_4 - C_{19} heteroaralkyl, and -Y- is C_1 - C_4 alkylene or a direct bond;

R_2 is phenyl, optionally substituted by one or more substituents, each of which is independently selected from

halo,

CF_3 ,

cyano,

amido or thioamido which is optionally mono- or di-N-substituted by C_1 - C_4 alkyl or the N atom of which forms a 5-7 membered heterocyclic ring optionally containing an additional hetero atom selected from O, S or N which N is optionally C_1 - C_4 alkyl C_1 - C_4 alkylcarbonyl or C_1 - C_4 alkylthiocarbonyl substituted,

carboxylate or thiocarboxylate optionally in the form of an optionally halo-substituted C_1 - C_{10} alkoxy, C_2 - C_{10} alkenoxy, C_2 - C_{10} alkynoxy, C_3 - C_7 cyclalkoxy, C_3 - C_7 cycloalkenoxy, aryloxy, arylalkoxy, heteroaryloxy or heteroarylalkoxy ester, optionally mono- or di- C_1 - C_4 alkyl-substituted- C_0 - C_1 alkyl optionally C_1 - C_4 alkyl- or C_3 - C_5 cycloalkyl-substituted-carbonyl or -thiocarbonyl,

optionally halo-substituted- C_1 - C_4 alkoxy, C_2 - C_4 alkenoxy, C_2 - C_4 alkynoxy, C_3 - C_5 cycloalkoxy or C_3 - C_5 cyclothioalkoxy,

optionally halo substituted C_1 - C_4 alkyl,

oxycarbonyl or optionally N- C_1 - C_4 alkyl-substituted aminocarbonyl both of which are optionally C_1 - C_4 alkyl or C_3 - C_5 cycloalkyl substituted (including thiocarbonyl analogues thereof),

optionally mono- or di- C_1 - C_4 alkyl-substituted- C_0 - C_1 alkylamine which is optionally mono-or di-N- C_1 - C_4 alkyl substituted,

optionally mono- or di- C_1 - C_4 alkyl-substituted- C_0 - C_1 alkyl optionally N- C_1 - C_4 alkyl-substituted amino-carbonyl or -thiocarbonyl,

optionally N- C_1 - C_4 alkyl-substituted amino-sulphinyl or -sulphonyl optionally substituted by

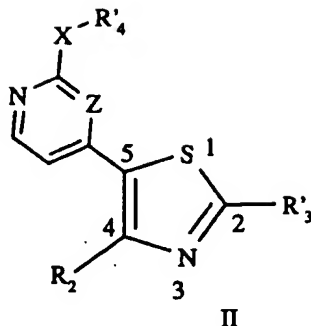
optionally mono- or di-N- C_1 - C_4 alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted, or
 sulphinyl or sulphonyl optionally substituted by
 optionally halo-substituted-C₁-C₄alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 optionally mono- or di-C₁-C₄alkyl-substituted amino,
 a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted;

R₃ is H, amino, C₁-C₁₀alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₈heterocycloalkyl, C₆-C₁₈aryl, or C₃-C₁₈heteroaryl each of which is optionally substituted by up to 4 substituents separately selected from C₁-C₄alkyl, halogen, halo-substituted-C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, C₁-C₄alkylthio, C₆-C₁₈aryl, C₃-C₁₈ heteroaryl, C₆-C₁₈arylC₁-C₄alkyl, C₃-C₁₈ heteroarylC₁-C₄alkyl, C₃-C₁₈heterocycloalkyl or optionally mono- or di-C₁-C₄alkyl substituted amino or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally a further hetero atom selected from O, S or N, all of which are further optionally substituted halo, hydroxy, C₁-C₄alkyl, C₁-C₄alkoxy or C₁-C₄alkoxycarbonyl;

R₄ is C₁-C₁₀alkyl, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, or C₃-C₁₂cycloalkyl optionally substituted by up to 3 substituents separately selected from C₁-C₄alkyl, halogen, halo-substituted- C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, C₁-C₄alkylthio, optionally mono- or di-C₁-C₄alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N,
 and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof

2. A compound according to claim 1 of formula II



wherein

Z is N or CH;

X is -NR₆-Y-, -O- or -S-,

where R₆ is H, C₁-C₄alkyl, C₃-C₈cycloalkyl, C₃-C₈cycloalkylC₁-C₃alkyl, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, C₇-C₁₉aralkyl or C₄-C₁₉heteroaralkyl, and -Y- is C₁-C₄alkylene or a direct bond ;

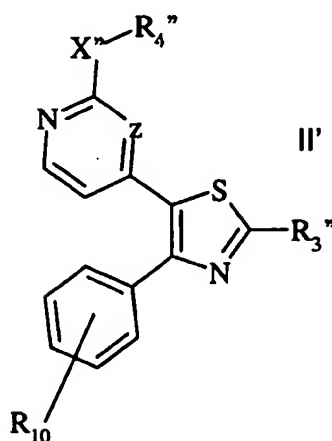
R₂' is phenyl, optionally substituted by one or more substituents, each of which is independently selected from halo, CF₃, cyano, amido or thioamido, carboxylate or thiocarboxylate, C₁-C₄alkoxy, C₁-C₄alkyl, or NH₂ which is optionally mono- or di-C₁-C₄alkyl substituted;

R₃' is H, C₁-C₁₀alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₈heterocycloalkyl, C₆-C₁₈aryl, or C₃-C₁₈heteroaryl each of which is optionally substituted by up to 4 substituents separately selected from C₁-C₄alkyl, halogen, halo-substituted-C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, C₁-C₄alkylthio, or optionally mono- or di-C₁-C₄alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N;

R₄' is C₆-C₁₈aryl, C₃-C₁₈heteroaryl, or C₃-C₁₂cycloalkyl each of which is optionally substituted by up to 4 substituents separately selected from C₁₋₄alkyl, halogen, halo-substituted-C₁₋₄alkyl, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylthio, or optionally mono- or di-C₁-C₄alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

3. A compound according to claim 2 of formula II'



wherein

R₄'' is phenyl or C₃-C₇cycloalkyl each of which is optionally mono-substituted by halogen, C₁-C₄alkyl, C₁-C₄alkoxy, hydroxy, trihalomethyl or optionally mono-or di-C₁-C₄alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N;

R₁₀ is halogen, cyano, amido, thioamido, amino or C₁-C₄alkyl;

R₃'' is H, C₁-C₄alkyl, phenyl, pyridyl, morpholinyl, piperidyl, piperazyl, or optionally mono- or di-C₁-C₄alkyl substituted amino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from C₁-C₄alkyl, halogen, hydroxy, C₁-C₄alkoxy, or optionally mono-or di-C₁-C₄alkyl substituted amino;

Z is N or CH and

X'' is -NH-Y'-, -O- or -S-, where Y' is -CH₂-, -CH₂-CH₂-, -CH(CH₃)- or a direct bond, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

4. A compound according to claim 2 selected from:

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-methyl-piperidine-1-yl)thiazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-NH-piperidine-1-yl)thiazole;

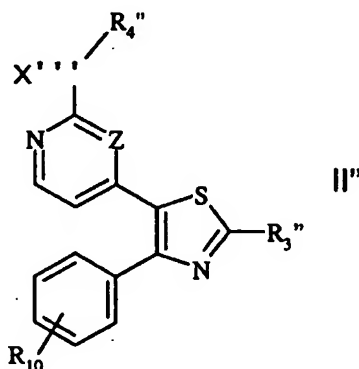
4-(4-Fluorophenyl)-2-(4-methylpiperidine-1-yl)-5-(2-[cyclopropyl-methyl]amino-4-

pyridinyl)thiazole and

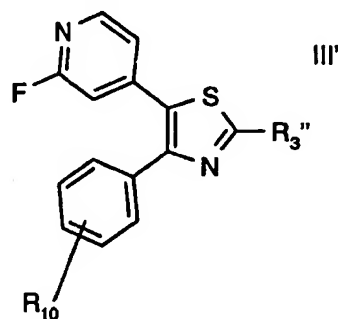
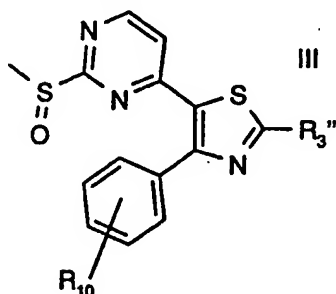
4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole;

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

5. A process for the preparation of a compound of formula II''

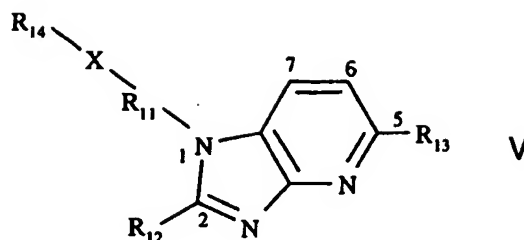


wherein R_3'' , R_4'' , R_{10} and Z are as defined in claim 3 and X''' is -NH-, which comprises reacting the corresponding precursor compound of formula III or III'



with the corresponding R_4'' -NH₂ amine, wherein R_3'' , R_4'' and R_{10} are as defined in claim 3, and thereafter, if desired, converting the compound of formula II'' obtained into a further compound of formula II'' or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof.

6. A compound according to claim 1 of formula V



wherein

R₁₁ is pyrimidyl;

X is -NR₆-Y-, -O- or -S-,

where R₆ is H, C₁-C₄alkyl, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, C₇-C₁₉aralkyl or C₄-C₁₉heteroaralkyl, and -Y- is C₁-C₄alkylene or a direct bond ;

R₁₂ is phenyl, optionally substituted by one or more substituents, each of which is independently selected from

halo,

CF₃,

cyano,

amido or thioamido which is optionally mono- or di-N-substituted by C₁-C₄alkyl or the N atom of which forms a 5-7 membered heterocyclic ring optionally containing an additional hetero atom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted,

carboxylate or thiocarboxylate optionally in the form of an optionally halo-substituted C₁-C₁₀alkoxy, C₂-C₁₀alkenoxy, C₂-C₁₀alkynoxy, C₃-C₇cyclalkoxy, C₅-C₇cycloalkenoxy, aryloxy, arylalkoxy, heteroaryloxy or heteroarylalkoxy ester, optionally mono- or di-C₁-C₄alkyl-substituted-C₀-C₁alkyl optionally C₁-C₄alkyl- or C₃-C₅cycloalkyl-substituted-carbonyl or -thiocarbonyl,

optionally halo-substituted-C₁-C₄alkoxy, C₂-C₁₀alkenoxy, C₂-C₁₀alkynoxy, C₃-C₇cycloalkoxy or C₃-C₅cycloalkoxy,

optionally halo substituted C₁-C₄ alkyl,

oxycarbonyl or optionally N-C₁-C₄alkyl-substituted aminocarbonyl both of which are optionally C₁-C₄alkyl or C₃-C₅cycloalkyl substituted (including thiocarbonyl analogues thereof),

optionally mono- or di-C₁-C₄alkyl-substituted-C₀-C₁alkylamine which is optionally mono-or di-N-C₁-C₄ alkyl substituted,
 optionally mono- or di-C₁-C₄alkyl-substituted-C₀-C₁alkyl optionally N-C₁-C₄alkyl-substituted amino-carbonyl or -thiocarbonyl,
 optionally N-C₁-C₄alkyl-substituted amino-sulphinyl or -sulphonyl optionally substituted by

optionally mono- or di-N-C₁-C₄alkyl-substituted amino,
 a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted, or
 sulphinyl or sulphonyl optionally substituted by

optionally halo-substituted-C₁-C₄alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 optionally mono- or di-N-C₁-C₄alkyl-substituted amino,

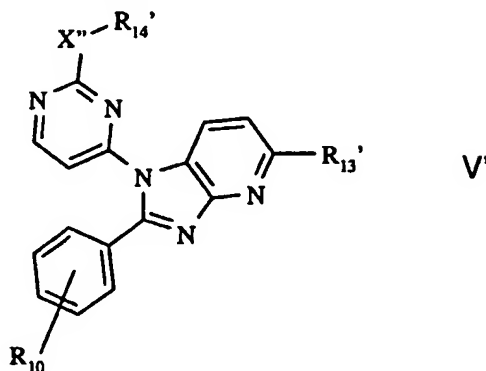
a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁-C₄alkyl C₁-C₄alkylcarbonyl or C₁-C₄alkylthiocarbonyl substituted;

R₁₃ is H, amino, C₁-C₁₀alkyl, C₃-C₁₀cycloalkyl, C₃-C₁₈heterocycloalkyl, C₆-C₁₈aryl, or C₃-C₁₈heteroaryl all optionally substituted by up to 4 substituents separately selected from C₁-C₄alkyl, halogen, halo-substitued-C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, C₁-C₄alkylthio, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, C₆-C₁₈arylC₁-C₄alkyl, C₃-C₁₈heteroarylC₁-C₄alkyl, C₃-C₁₈heterocycloalkyl or optionally mono- or di-N-C₁-C₄alkyl substituted amino all of which are optionally substituted by halo, hydroxy, C₁-C₄alkyl, C₁-C₄alkoxy or C₁-C₄alkoxycarbonyl;

R₁₄ is C₁-C₁₀alkyl, C₆-C₁₈aryl, C₃-C₁₈heteroaryl, or C₃-C₁₂cycloalkyl optionally substituted by up to 3 substituents separately selected from C₁-C₄alkyl, halogen, halo-substitued-C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy, C₁-C₄alkylthio, optionally mono- or di-N-C₁-C₄alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

7. A compound according to claim 6 of formula V'



wherein

R_{14}' is phenyl or C_3 - C_7 cycloalkyl each of which is optionally mono-substituted by halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, hydroxy, trihalomethyl optionally mono- or di- N - C_1 - C_4 alkyl substituted amino, or by N -heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N;

R_{10} is halogen, CF_3 , C_1 - C_4 alkyl or C_1 - C_4 alkoxy;

R_{13}' is pyridyl, pyrimidyl, piperazinyl, piperidinyl, NR_9R_{10} , $-CH_2OH$, $CH_2NR_{15}R_{16}$, $-CH_2CH_2R_{15}R_{16}$, or Het- C_1 - C_4 alkyl-,

wherein

R_9 and R_{10} are separately selected from H, C_1 - C_4 alkyl, C_6 - C_{18} aryl, C_3 - C_{18} heteroaryl, C_6 - C_{18} aryl C_1 - C_4 alkyl, C_3 - C_{18} heteroaryl C_1 - C_4 alkyl all of which are optionally substituted by halo, hydroxy, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkoxycarbonyl,

R_{11} and R_{12} are separately selected from H or C_1 - C_6 alkyl, and

Het is N -heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom (e.g. O, S or N)

X'' is $-NH-Y'$ -, $-O-$ or $-S-$, where Y' is $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$ or a direct bond, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

8. A compound according to claim 6 selected from:

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(N,N-diethylamino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(morpholino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(isopropylamino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(pyrrolidino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(3-pyridyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-pyridyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-piperidinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-methyl-4-piperidinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-(2-hydroxy-2-methyl)propyl-4-piperidinyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(benzylamino)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(morpholino)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(3-fluorophenyl amino)imidazo[4,5-b]pyridine;

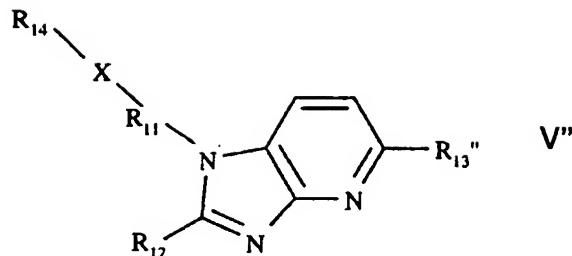
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(pyridyl-4-amino)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-ethoxycarbonyl piperidine-4-amino)imidazo[4,5-b]pyridine, and

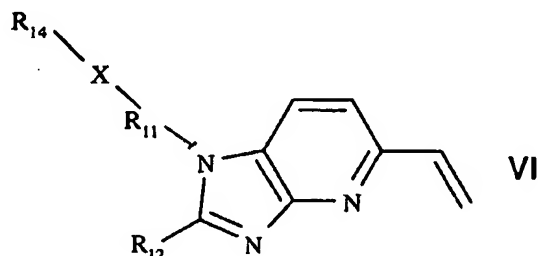
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidine-4-amino)imidazo[4,5b]pyridine.

9. A process for the production of

(i) an Agent of the Invention of formula V''

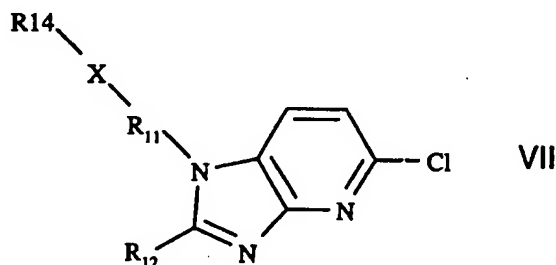


wherein R_{11} , R_{12} , R_{14} and X are as previously defined and R_{13}'' is $-\text{CH}_2-\text{CH}_2\text{NR}_{15}\text{R}_{16}$ or $-\text{CH}_2-\text{CH}_2\text{-Het}$ wherein R_{15} , R_{16} and Het are as previously defined comprising reacting a corresponding vinyl precursor of formula VI



wherein R_{11} , R_{12} , R_{14} and X are as previously defined with the corresponding amine of formula $\text{HNR}_{15}\text{R}_{16}$ or N-heterocycloalkyl ring compound;

- (ii) an Agent of the Invention of formula V wherein R_{13} is aryl or heteroaryl comprising arylation or heteroarylation of a compound of formula VII

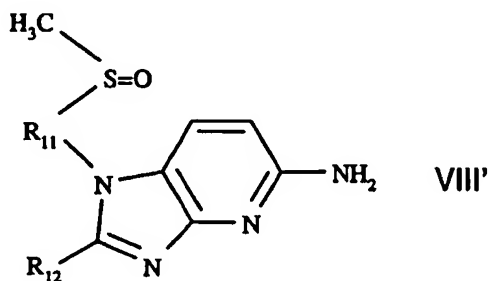


wherein R_{11} , R_{12} , R_{14} and X are as previously defined;

- (iii) an Agent of the Invention of formula V wherein R_{13} is -N-heterocycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -NH-($\text{C}_1\text{-C}_4$ alkyl)-heterocycloalkyl, -NH-($\text{C}_1\text{-C}_4$ alkyl)-aryl, -NH-($\text{C}_1\text{-C}_4$ alkyl)-heteroaryl, or -NH-($\text{C}_1\text{-C}_4$ alkyl)-heterocycloalkyl comprising

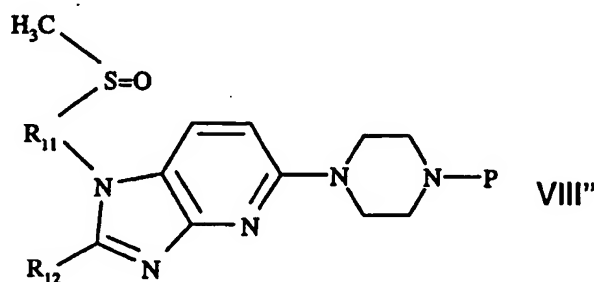
coupling a corresponding chloroprecursor compound of formula VII, as defined above, with the corresponding N-heterocycloalkyl compound or amine;

- (iv) an Agent of the Invention of formula V in which R_{13} is $-NH_2$, comprising reacting the corresponding methyl sulphonyl compound of formula VIII'



wherein R_{11} , and R_{12} are as previously defined, with the corresponding amine of formula $R_{14}-NH_2$, and

- (v) an Agent of the Invention of formula V in which R_{13} is piperazinyl, comprising reacting a corresponding methylsulphonyl compound of formula VIII''



wherein R_{11} and R_{12} are as previously defined and P is an N protecting group, with the corresponding amine of formula $R_{14}-NH_2$.

10. A method of inhibiting production of soluble TNF, especially $TNF\alpha$, or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of a compound according to claim 1.

11. A compound according to claim 1 for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.
12. A pharmaceutical composition comprising a compound according to claim 1 in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.
13. Use of a compound according to claim 1 in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/EP 00/10528

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D417/04 C07D471/04 A61K31/437 A61K31/4436
//(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 69848 A (MERCK & CO., INC., USA) 23 November 2000 (2000-11-23) the whole document ---	1-13
E	WO 00 63204 A (NOVARTIS A.-G., SWITZ.;NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.) 26 October 2000 (2000-10-26) the whole document ---	1-13
E	WO 00 64894 A (KANZAKI NAUYUKI ;MIWATASHI SEIJI (JP); OHKAWA SHIGENORI (JP); TAKE) 2 November 2000 (2000-11-02) the abstract, whole document and examples --- -/--	1-13

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

15 January 2001

Date of mailing of the international search report

30. 01. 01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

Intern Application No

PCT/EP 00/10528

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 05878 A (MERCK & CO INC ;LASZLO STEPHEN E DE (US); MANTLO NATHAN B (US); PO) 20 February 1997 (1997-02-20) see especially the examples and definition of Ra ----	1-13
P,Y	WO 00 09506 A (HOKURIKU PHARMACEUTICAL ;AOYAMA MAKOTO (JP); KATO KEN ICHI (JP); S) 24 February 2000 (2000-02-24) the whole document ----	1-13
A	US 5 739 143 A (ADAMS JERRY LEROY ET AL) 14 April 1998 (1998-04-14) the whole document ----	1-13
Y	WO 95 13067 A (SMITHKLINE BEECHAM CORP ;ADAMS JERRY LEROY (US); GALLAGHER TIMOTHY) 18 May 1995 (1995-05-18) the whole document -----	1-13

INTERNATIONAL SEARCH REPORT

In: International application No.
PCT/EP 00/10528

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/10528

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0069848	A	23-11-2000	NONE	
WO 0063204	A	26-10-2000	NONE	
WO 0064894	A	02-11-2000	NONE	
WO 9705878	A	20-02-1997	AU 699148 B	26-11-1998
			AU 6769196 A	05-03-1997
			CA 2228050 A	20-02-1997
			EP 0871444 A	21-10-1998
			JP 11510511 T	14-09-1999
			US 5837719 A	17-11-1998
WO 0009506	A	24-02-2000	JP 2000119271 A	25-04-2000
			AU 5197499 A	06-03-2000
US 5739143	A	14-04-1998	US 5658903 A	19-08-1997
			AU 5703398 A	03-07-1998
			EP 0961618 A	08-12-1999
			US 5869660 A	09-02-1999
			WO 9825619 A	18-06-1998
			AU 699646 B	10-12-1998
			AU 6272696 A	30-12-1996
			BR 9608591 A	05-01-1999
			CA 2223533 A	19-12-1996
			CN 1192147 A	02-09-1998
			CZ 9703925 A	16-09-1998
			EP 0831830 A	01-04-1998
			HU 9802259 A	28-09-1999
			JP 11513017 T	09-11-1999
			NO 975716 A	04-02-1998
			PL 323916 A	27-04-1998
			WO 9640143 A	19-12-1996
WO 9513067	A	18-05-1995	EP 0727998 A	28-08-1996
			JP 9505055 T	20-05-1997